THE American JOURNAL OF Surgery

SIXTY-SEVENTH YEAR OF PUBLICATION

Symposium on Surgery of the Ductless Glands

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MARCH 1950

MARCH 1958

THE American JOURNAL OF Surgery

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The American Journal of Surgery is published monthly by The American Journal of Surgery, Inc., 11 East 36th Street, New York 16, N. Y. Yearly Subscription, $15.00 U. S. A.; $16.00 Canada; $17.00 Foreign including Pan-American Countries. Single Numbers $2.00; Special and Symposium Numbers $4.00. Second-class mail privileges authorized at New York, N. Y. with additional second-class mail privileges authorized at York, Pa.—New Series, Volume 95, No. 3.
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MANUSCRIPTS: All manuscripts should be typewritten double space and addressed to the Editorial Office of the Journal, 11 East 36th Street, New York 16, N. Y. The top should be indicated on the back of each photograph. *Style for bibliography:* DOE, J. J. Modern technics in surgery. Am. J. Surg., 5:93, 1950.

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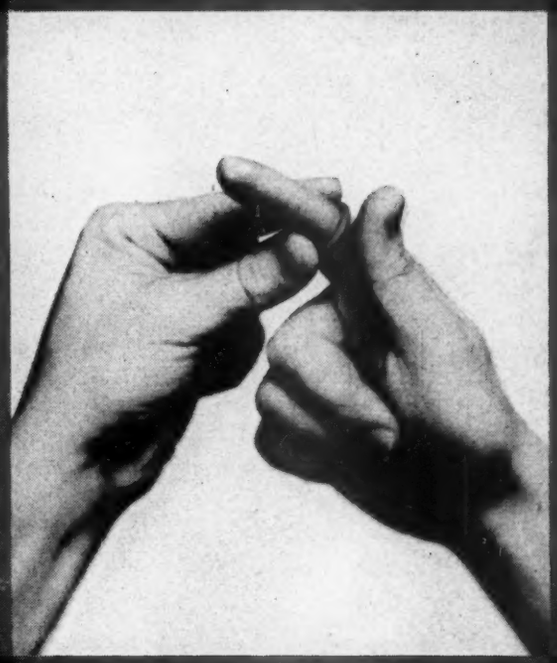

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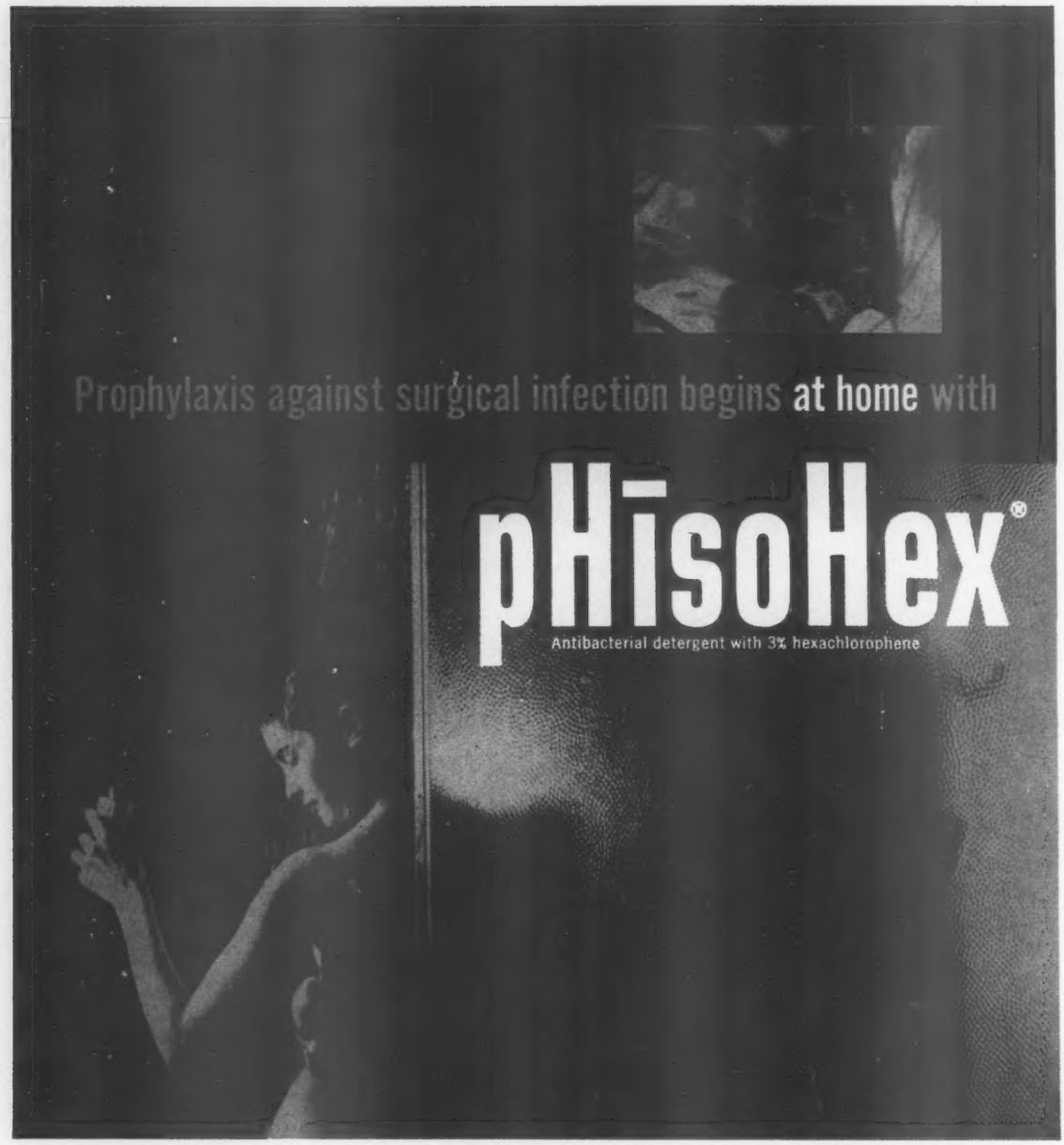
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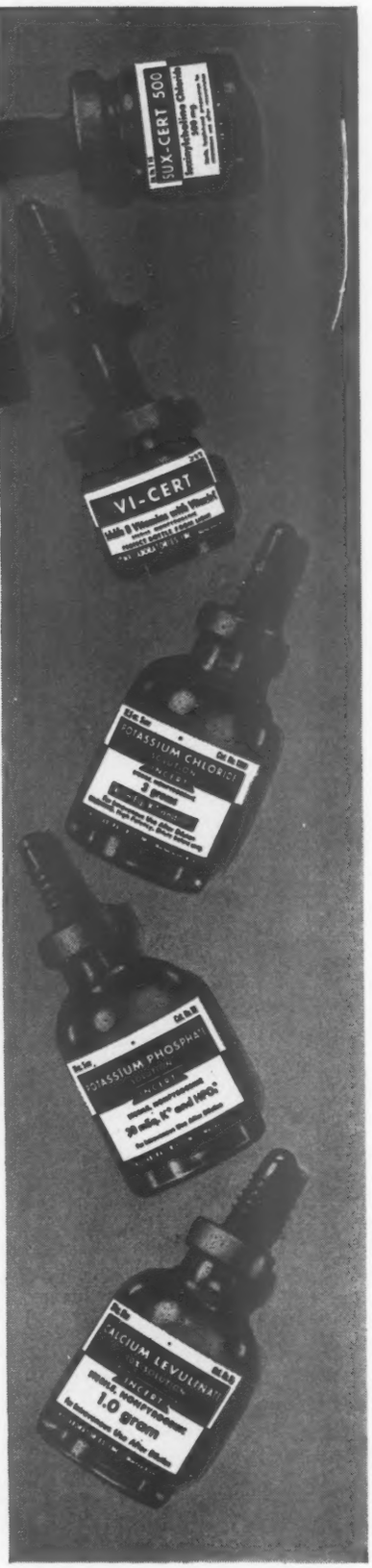

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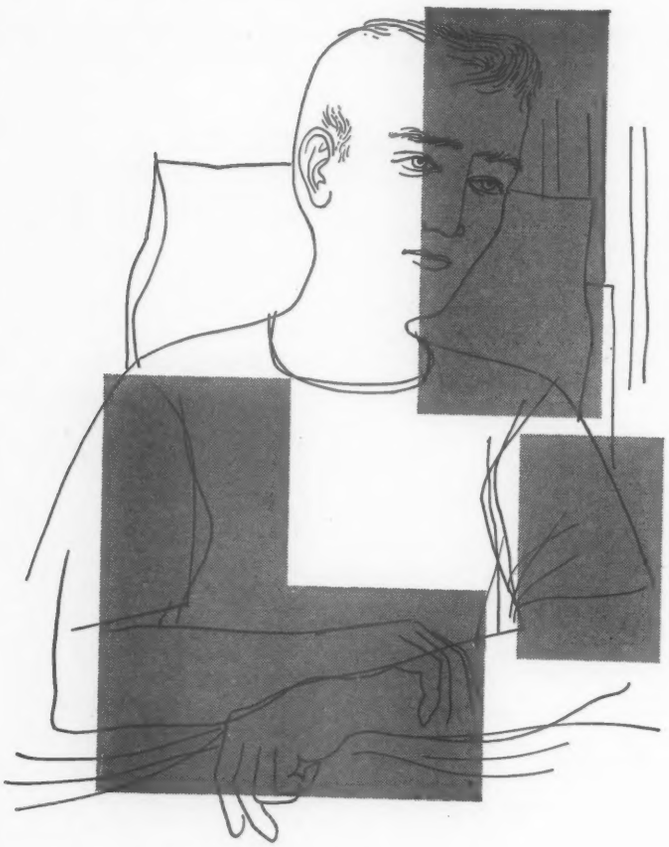

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1. *Rushia, E. L.: Preliminary report on the use of meprobamate for pre-anesthetic sedation. J.M.A. Georgia* **46**:*93, March 1957.*
2. *Lamphier, T. A.: The role of meprobamate in postoperative surgical care. Ann. New York Acad. Sc.* **67**:*810, May 9, 1957.*
3. *Kern, E. C.: Preoperative sedation with meprobamate (Miltown) in surgery of eye, ear, nose and throat. Eye, Ear, Nose & Throat Month.* **36**: *408, July 1957.*

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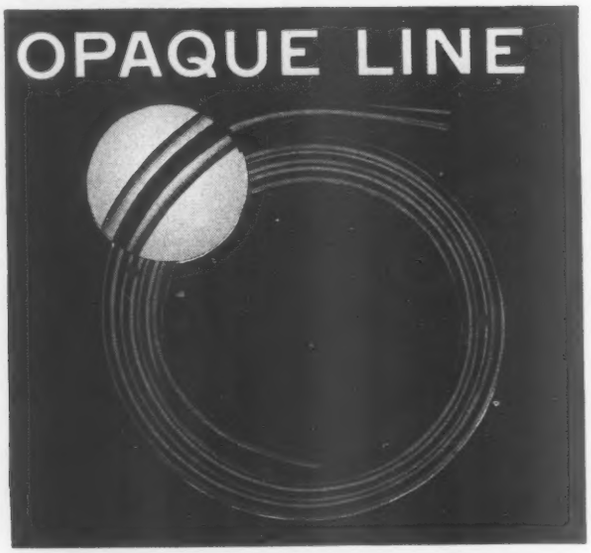

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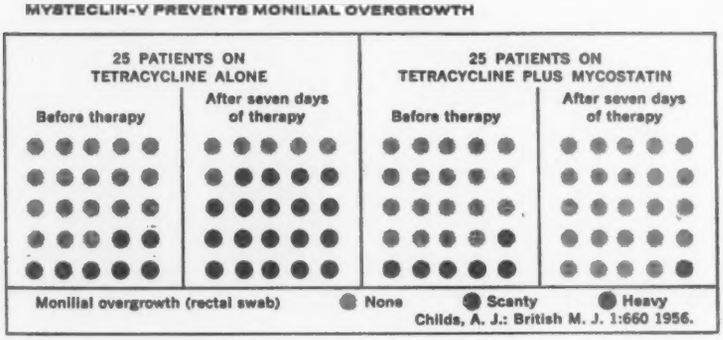

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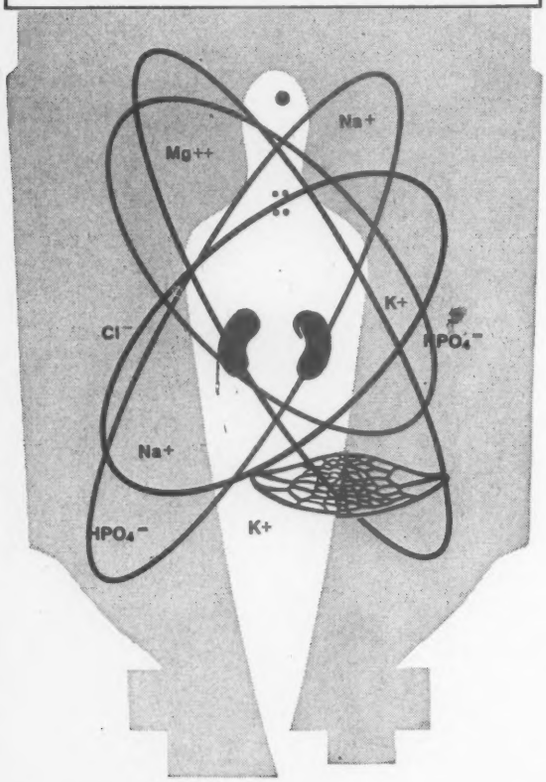

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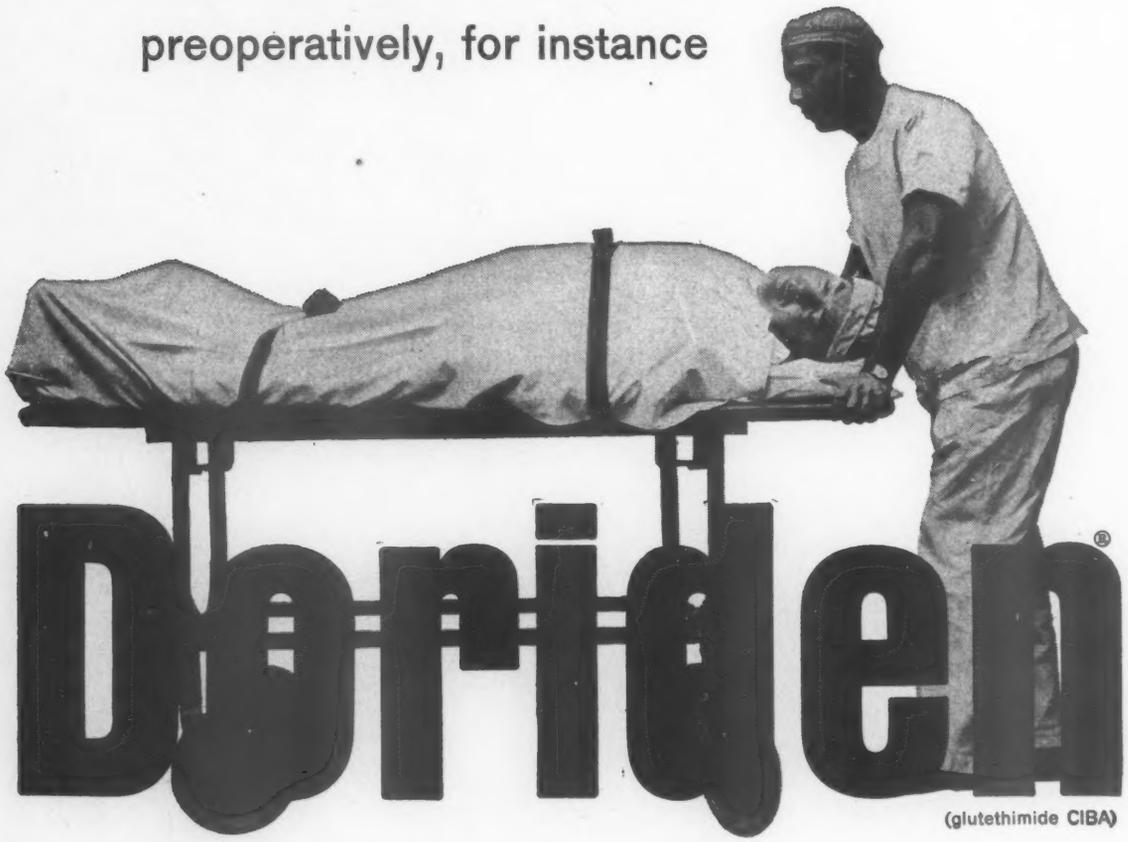

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1. Matlin, E.: M. Times 84:68 (Jan.) 1956.

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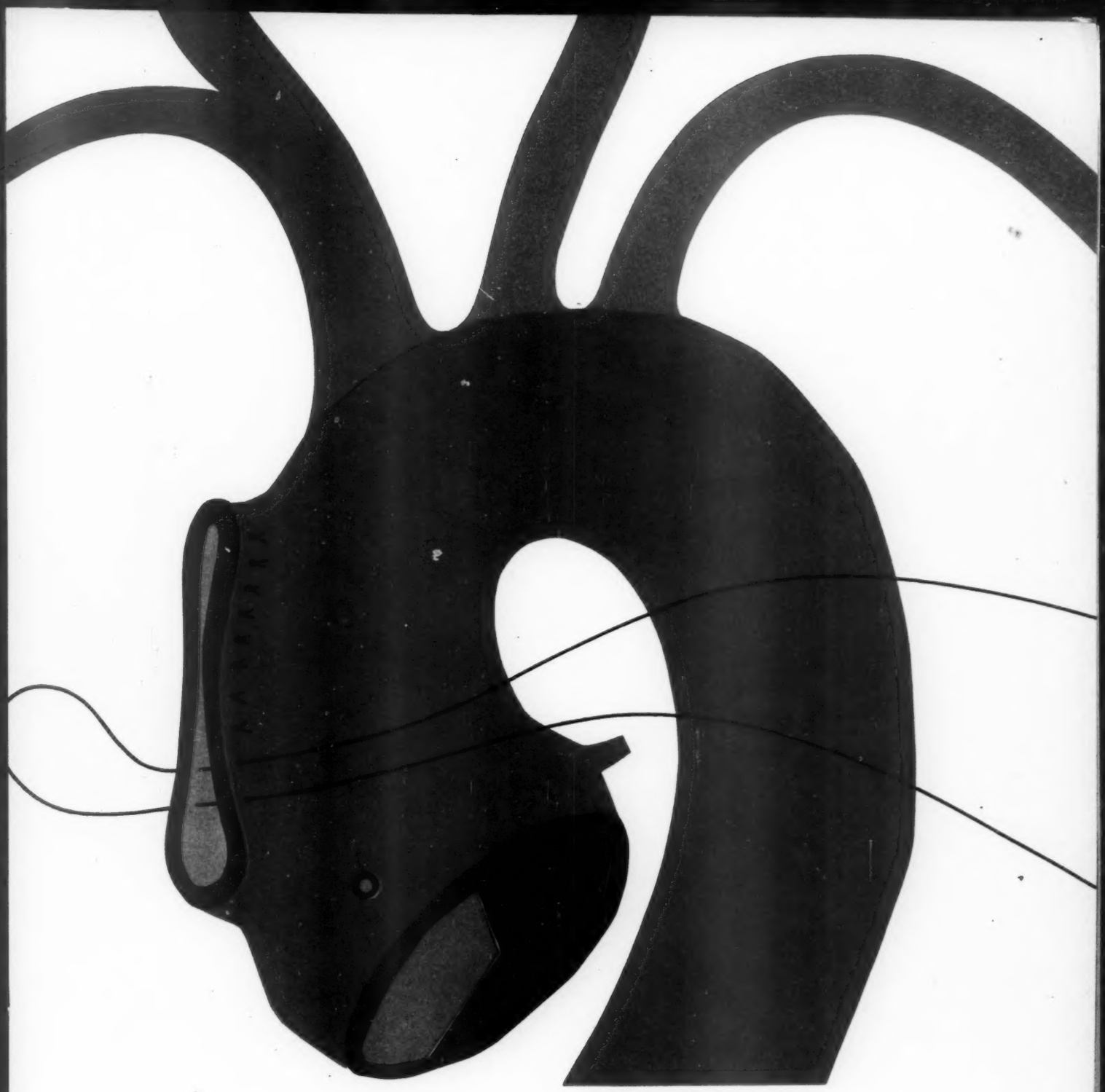

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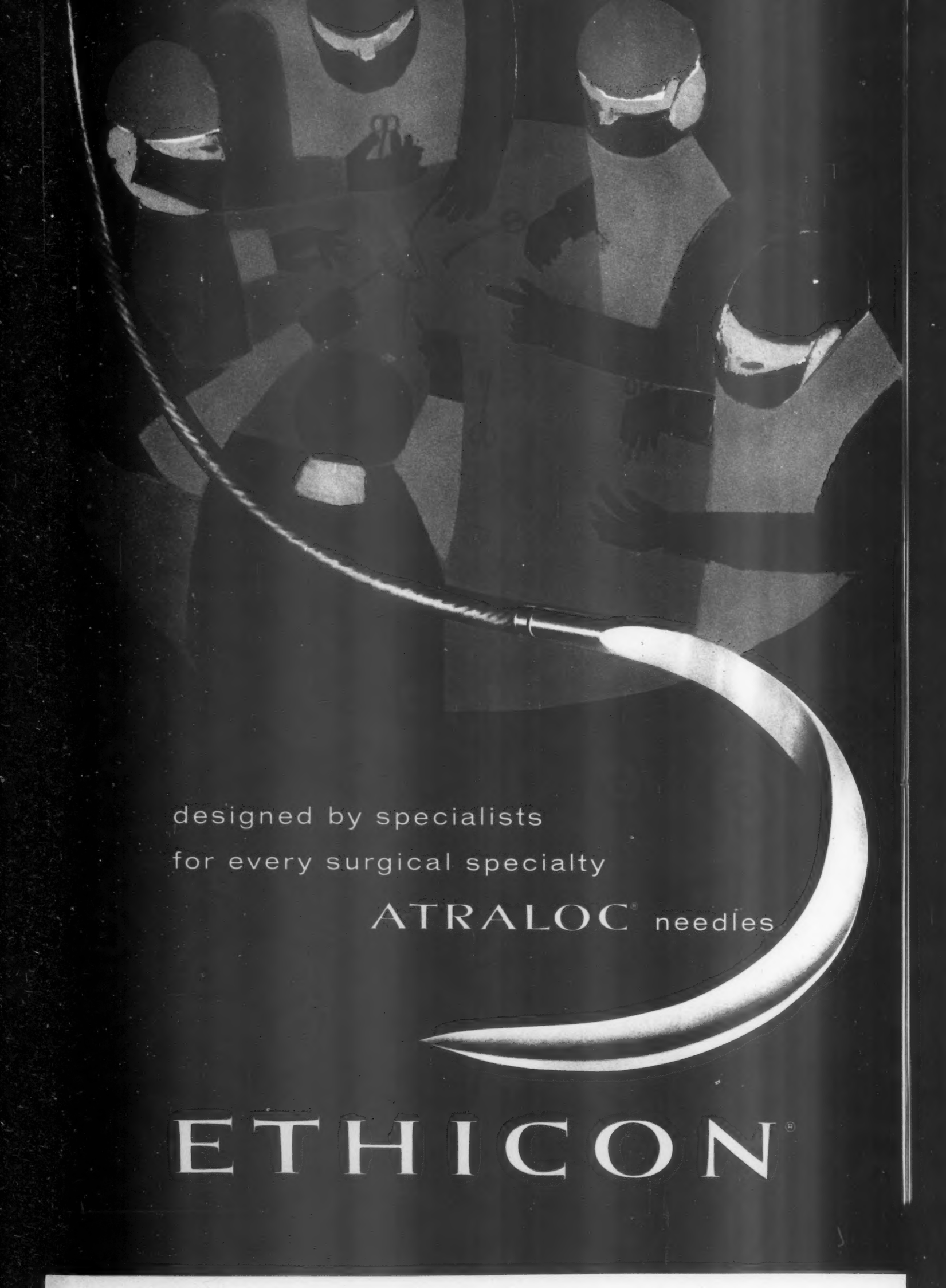
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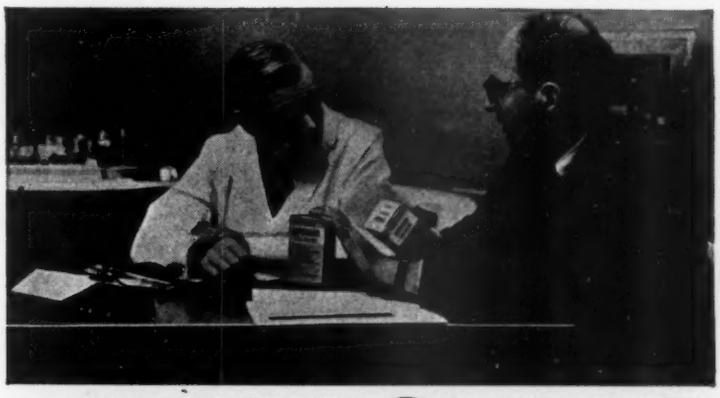

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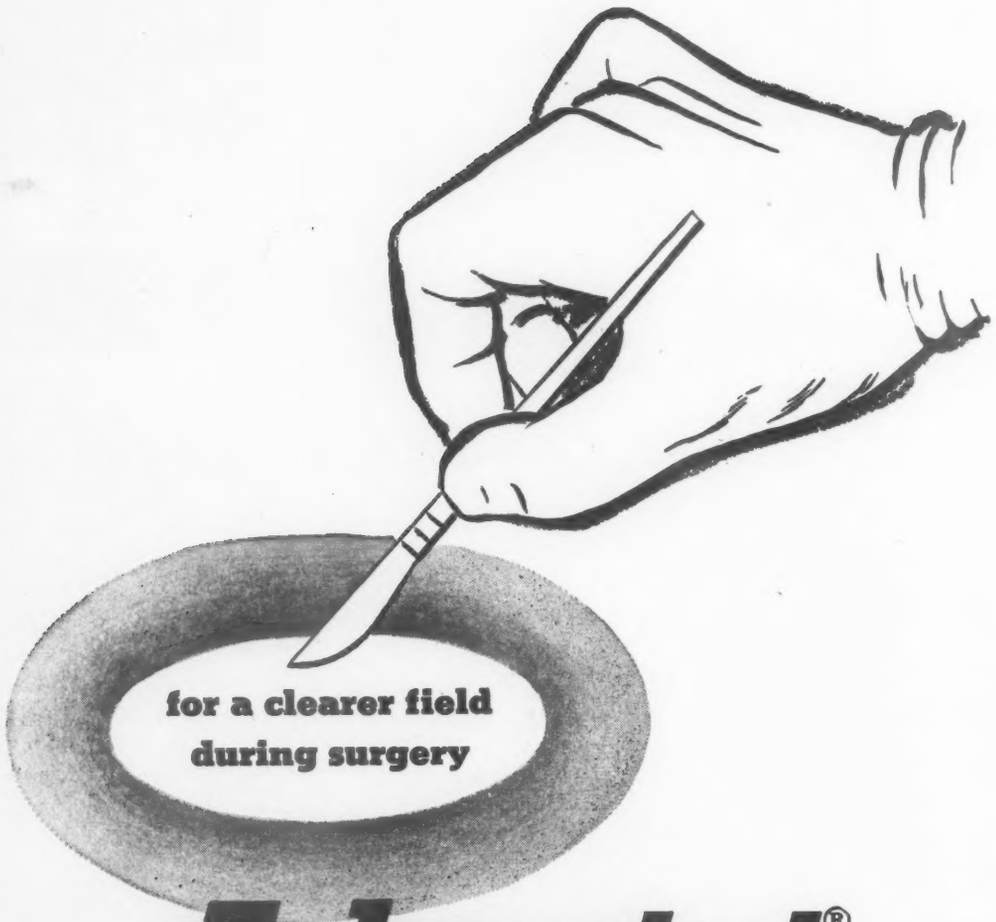

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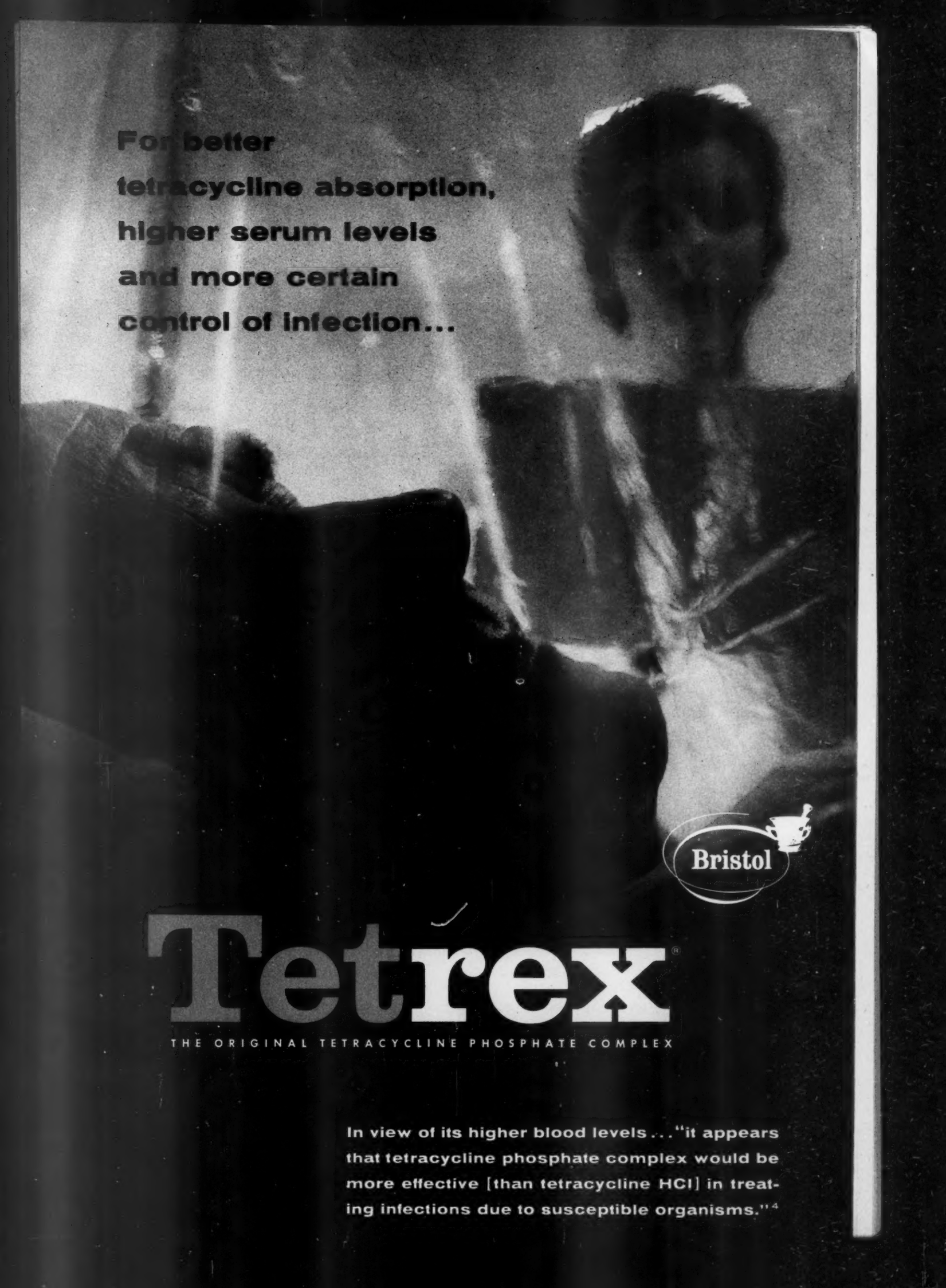
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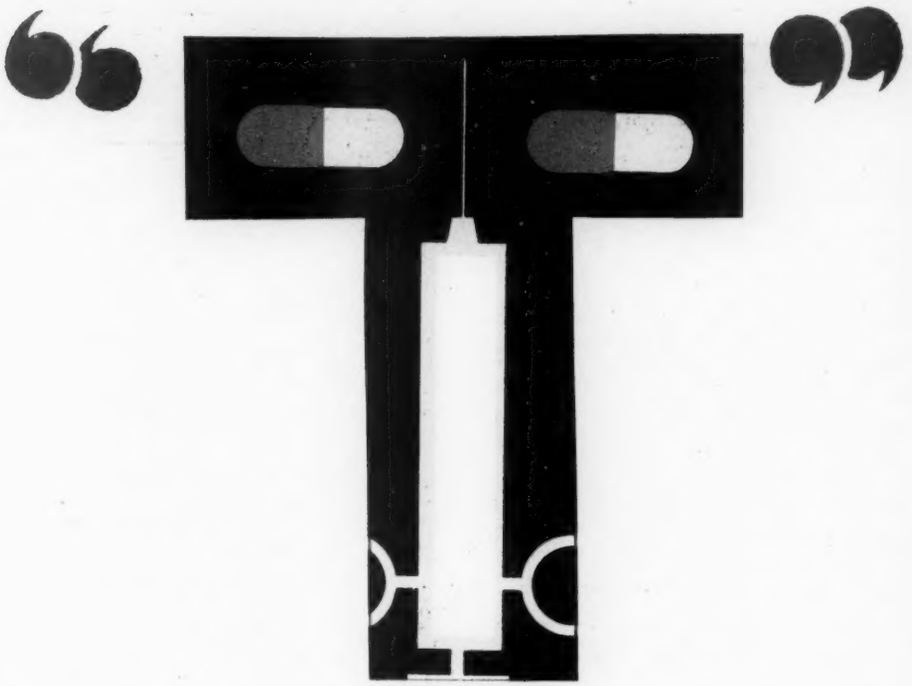

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"The advantages of higher blood and tissue levels of tetracycline in combating infections with susceptible bacteria are significant."[1]

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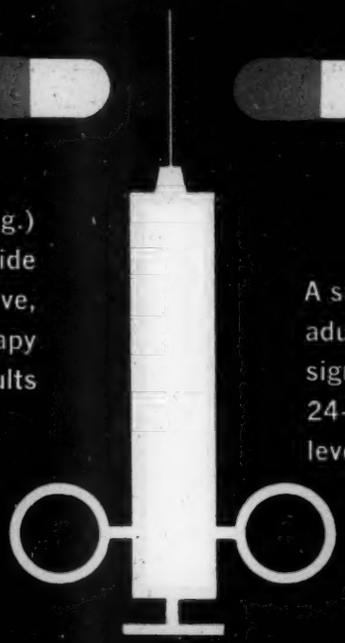
References: 1. Cronk, G. A., Naumann, D. E., and Casson, K.: Fifth Annual Symposium on Antibiotics, Washington, D. C., Oct. 2-4, 1957. 2. Dube, A. H.: *Ibid.* 3. Portney, B., Draper, T., and Wehrle, P. F.: *Ibid.* 4. Shidlovsky, B. A., Prigot, A., Maynard, A. de L., Felix, A. J., and Hjelt-Harvey, I.: *Ibid.* 5. Cronk, G. A., and Naumann, D. E.: Ant. Med. & Clin. Ther. 4:166, 1957. 6. Prigot, A., Shidlovsky, B. A., and Felix, A. J.: *Ibid.* 4:487, 1957. 7. Pulaski, E. J., and Isokane, R. K.: *Ibid.* 4:408, 1957. 8. Putnam, L. E.: *Ibid.* 4:470. 1957. 9. Rein, C. R., and Fleischmajer, R.: *Ibid.* 4:422, 1957. 10. Welch, H., Lewis, C. N., Staffa, A. W., and Wright, W. W.: *Ibid.* 4:215, 1957. 11. Pulaski, E. J.: Practitioner 179:465, 1957.

"...an improvement and ultimate replacement for the older tetracycline hydrochloride."[1]



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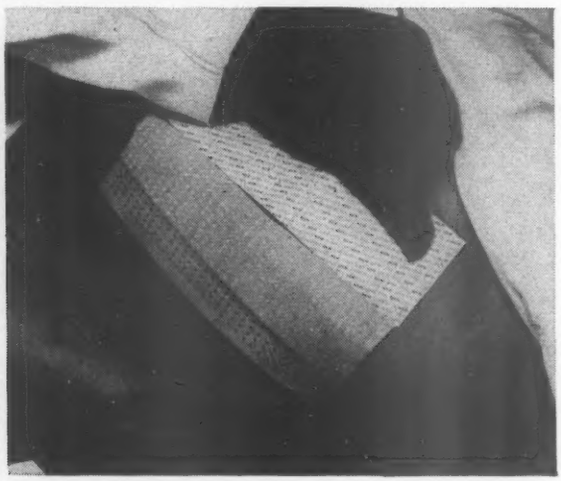

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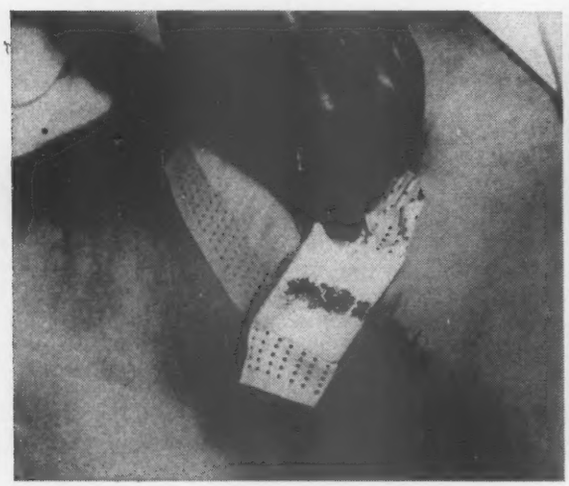

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1. Pulaski, E. J., and Isokane, R. K.: Surg., Gynec. & Obst., 104:310, March 1957.
2. Petersdorf, R. G., Curtin, J. A., and Bennett, I. L.: Arch. Int. Med. 100:927, December 1957.

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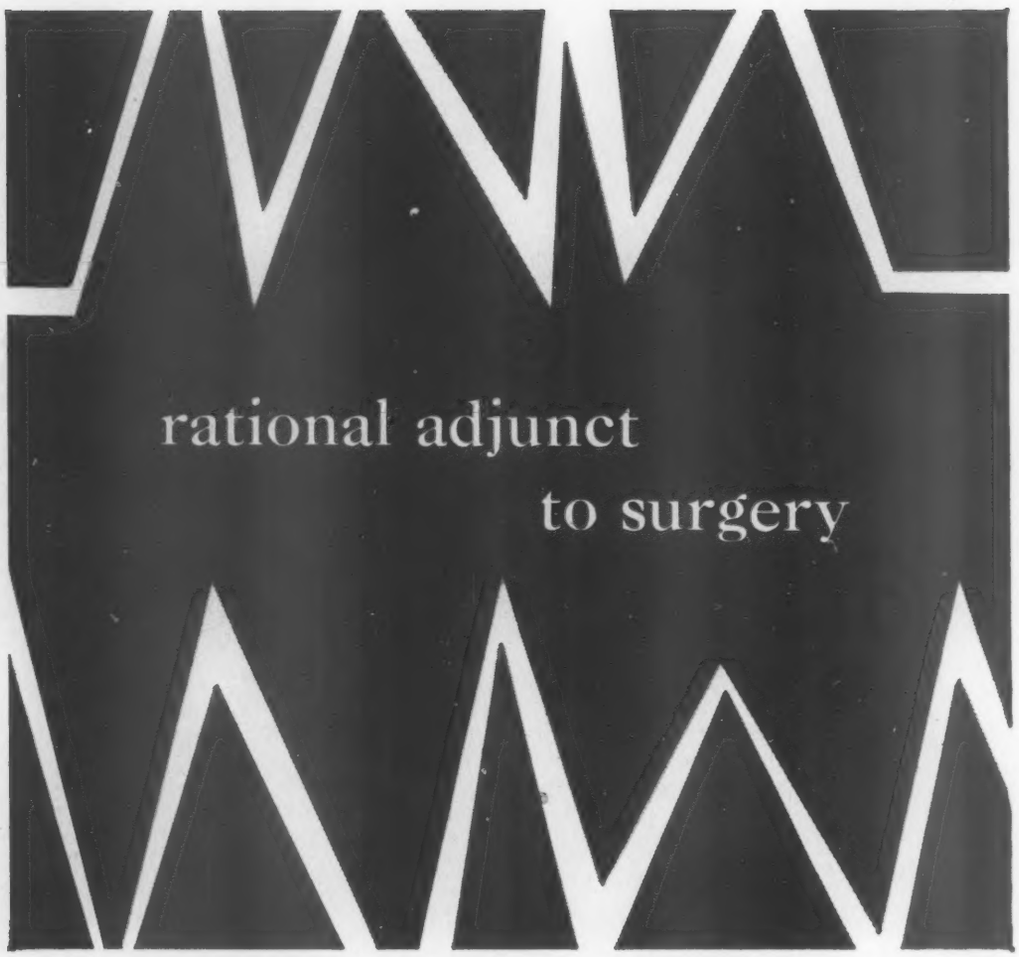

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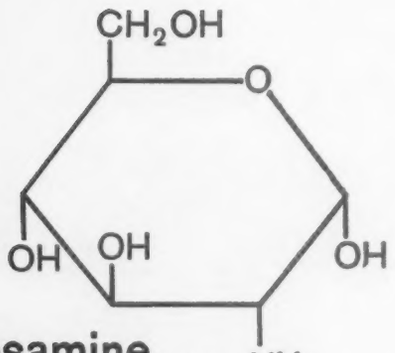

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The American Journal of Surgery

VOLUME 95 MARCH 1958 NUMBER THREE

SYMPOSIUM ON SURGERY OF THE DUCTLESS GLANDS

Introduction to Symposium

THE Third (Boston University) Surgical Service of the Boston City Hospital held its First Annual Surgical Seminar in the Spring of 1954. This proved to be such an overwhelming success that it was decided to hold these annually, since the value of seminars to a hospital are many.

They stimulate an exchange of ideas of surgical knowledge and technic with established surgeons from all parts of the country. They afford the opportunity of meeting people who have a common interest in a specialized field whose only contact would otherwise be limited to written articles and books. Also, the talks and discussions—with audience participation—disseminate surgical knowledge to the attending staff, house officers and medical students not only of the Boston University Service but also of the other teaching services at the Boston City Hospital.

The Third Surgical Service Symposiums consist of papers on selected subjects. Prominent physicians from various parts of the country as well as from Boston who specialize in these fields are invited to participate. The subject of our First and Second Seminars was "Peripheral Vascular Disease" and the Third, "Modern Developments in Surgery." The Fourth, the proceedings of which are included in this issue, featured "Surgery of the Ductless Glands." This topic was chosen in order to focus attention on an unusual group of diseases which are not commonly encountered.

The success of these Seminars depends on many. The Third Surgical Service extends its thanks and appreciation to Dr. E. Everett O'Neil, Surgeon-in-Chief Emeritus, who served as moderator and who is a constant stimulus to the success of the program; to the many speakers who participated in our past Seminars; and in particular to the speakers of the Fourth Annual Seminar who prepared papers not only for presentation but also for publication.

The Third Surgical Service is grateful to *The American Journal of Surgery*, which by publishing these proceedings affords the opportunity for all who attended the seminar to obtain a personal annotation and also for those individuals who could not be present the privilege of sharing in the knowledge imparted. Information concerning these "Proceedings" may be obtained from the Director of the Service.

The Fifth Annual Seminar of the Third (B.U.) Surgical Service will be held at the Boston City Hospital on April 9, 1958, from 9:30 A.M. to 5:30 P.M. The topic will be "Surgery of the Biliary Tract." All physicians and medical students are invited to attend.

JOHN J. BYRNE, M.D.,
Boston, Massachusetts

Ovarian Tumors

WITH SPECIAL REFERENCE TO SOME UNEXPECTEDLY GOOD OUTCOMES IN THE TREATMENT OF CANCER OF THE OVARY

GEORGE V. SMITH, M.D., *Brookline, Massachusetts*

From the Department of Gynecology, Harvard Medical School, Boston, Massachusetts, and The Free Hospital for Women, Brookline, Massachusetts.

I CAN say nothing new or exciting about ovarian tumors, so, in accordance with Dr. Byrne's suggestion, I shall cover briefly some of the usual aspects and then describe the thus far happy outcome of "later look" surgery in three of four patients who had ovarian cancer.

Classification. The ovaries of females of the human species are notable for their totipotentiality in the genesis of tumors. This is, perhaps, not surprising considering what their eggs are capable of becoming. A full classification of ovarian tumors would list about thirty-five different types, and even this would not cover all the possible variants; but for practical purposes the following simple classification is adequate:

1. The serous cystadenomas, benign and malignant, comprise about 35 per cent of all ovarian tumors.

2. The mucinous cystadenomas, benign and malignant, make up about 25 per cent.

3. The cystic teratomas of adult types of tissues, i.e., the dermoid cysts, make up about 25 per cent.

4. Fibromas account for about 7 per cent.

5. Granulosa-theca cell tumors (also called feminizing mesenchymomas) comprise about 2 per cent.

6. The remaining 6 per cent consist of a variety of benign and malignant new growths. The benign are such rarities as leiomyoma, adenomyoma, adenoma, Brenner and adrenal cortical–like tumor. The malignant are the undifferentiated carcinoma, carcinosarcoma, sarcoma, hypernephroma, mesonephroma, dysgerminoma and the teratomas of embryonal types of tissues. The rare arrhenoblastoma and ovarian struma, both of which may be benign or malignant, go in this 6 per cent group along with the uncommon vascular tumors. Thus we are ordinarily concerned with the serous and mucinous cystadenomas and the simple dermoid cysts. It is of considerable comfort to know that at the very most not more than 25 per cent of the various reported series of ovarian new growths are malignant.

Incidence. It has been estimated that between babyhood and the age of eighty a human female has roughly a 1 per cent chance of having a benign ovarian tumor develop, and considerably less than a 1 per cent chance of having an ovarian malignancy. Most of this low incidence is discovered between the ages of forty and seventy. Interesting in this connection is that the incidence of ovarian tumors in women coming to the Free Hospital for Women during the past fifty-five years is 1.8 per cent, which includes a little less than three-tenths of 1 per cent of malignancy.

Many of us like to think that we are saving an occasional patient from the later development of a benign neoplasm or cancer when we remove normal ovaries while performing hysterectomy in women near and after the age of forty. Parenthetically, the pathologist surprisingly often reports evidence of endometriosis and other beginnings of potentially neoplastic change in these grossly normal ovaries; but according to epidemiological estimates, only one a year of 2,500 of our female population has an ovarian malignancy. Therefore our relatively few prophylactic ovariectomies are, perhaps, not accomplishing much. On the contrary, in these days when scientific accuracy and statistical significance are required for the justification of procedures, and when simultaneously emphasis is being placed on the intangibles and immeasurables of climacteric psychology and

on the possible effect of ovarian hormone withdrawal as regards later osteoporosis and vascular disease, one gets a feeling of guilt that he may be doing actual harm by performing prophylactic ovariectomy in premenopausal women.

The fact remains, however, that 4 per cent of those with ovarian malignancies have had previous hysterectomies with ovarian conservation after the age of thirty-nine. It is after this age that 87 per cent of the malignancies occur. Four per cent represents a small number of patients, but with the ultimate mortality of this disease being at the very least 75 per cent, it is natural to lean toward prophylactic ovariectomy at hysterectomy during the premenopausal and menopausal era. The question which cannot yet be answered with authority is whether the number of ovariectomies required to prevent the development of one cancer and a few benign tumors may wreak more ultimate harm. For what they may be worth, here are my thoughts on the subject after a generation of experience in gynecology: The castration climacteric is, in itself, not at all disastrous mentally. Symptom-producing osteoporosis is no more common in women without their ovaries. I have not been impressed by vascular disease in castrated women. I have no figures to support these statements, and they may in time be proved wrong, but I can state with some statistical support that the most common cancer in women, cancer of the breast, with its highest incidence between the ages of forty and sixty, is likely to be slower in its growth in the absence of the ovaries.

In passing, I would point out an interesting inconsistency. Others (and I) who have practiced prophylactic ovariectomy during abdominal hysterectomy (with the patient's acquiescence, of course) have usually left the ovaries alone during vaginal hysterectomy, obviously because of the greater technical difficulty involved. This inconsistency amused me for some years. It now bothers me because in the past eighteen months two of our patients have been found to have hopeless ovarian cancer one to two years after their ovaries had been described as normal at vaginal hysterectomy.

Complaints: Diagnosis. As is known, there are no complaints which specifically indicate the presence of an ovarian tumor in its earliest stages. The familiar variable complaints are due to growth which has progressed beyond the early stage. Women who have not had periodic examinations continue to show up with large tumors or bad cancers; yet paradoxically, it is a relatively rare experience to find a tumor among those who year after year faithfully report for their six-to-twelve month checkups.

To make diagnoses earlier in a really significant number of cases would present a tremendous epidemiological problem, not to mention the problem of medical manpower. The best we can do, therefore, is to continue to urge as many women as possible to demand periodic general and pelvic examinations. In addition, I would emphasize that the ovaries be included in a complete intraperitoneal examination whenever the abdomen is opened, unless this procedure is clearly contraindicated by the condition for which the surgery is undertaken. I am thinking of a recent patient with extensive ovarian cancer who had undergone cholecystectomy and appendectomy fifteen months previously, and wonder whether the cancer might have been discovered then.

How large must an ovary be to require surgical investigation? I would say investigate any enlargement in a woman past the menopause; moreover, even though no enlargement can be felt in a postmenopausal woman with bleeding from a hormonal-stimulated endometrium, one may be certain of the presence of neoplastic ovarian change, this being almost always benign. Prior to the menopause a diameter of 5 cm. or more is likely to mean something other than a simple follicle or luteal cyst, and hence be an indication for surgery. Enlargements of less than 5 cm. before the menopause may be found to have regressed or remained unchanged as they are followed up. And may I add the warning that ovarian neoplasms are occasionally mistaken for asymptomatic leiomyomas with regrettable delay of therapy.

In considering ovarian tumors our thoughts always revert to the malignacies. Only about 5 per cent of the malignancies are 5 cm. or less at the time of diagnosis, and most of these are discovered at operations for something else. Although the results of treatment in these cases are considerably better, namely, about 70 per cent of five-to-fifteen year survival, they still leave much to be desired. It is likely that these small cancers were malignant from their incipience; in fact, we know from unhappy experiences that extensive malignancy can de-

velop in the absence of any palpable ovarian enlargement.

Diagnosis: Treatment. To this point we have been considering ovarian enlargements as the first stage in diagnosis. It is in the operating room, of course, that the final diagnosis is obvious or is made with the help of the pathologist. Because of the possible dangers from spilling their contents in the peritoneal cavity, the effort to avoid rupturing or breaking tumors during removal is considered desirable. With benign tumors the conservation of normal ovarian tissue is the keynote of surgical management so long as there is reasonable certainty that normal tissue is being conserved. Further neoplastic development is of very rare occurrence in these patients. Despite this knowledge, associated pelvic disease and the apprehension of further ovarian neoplasia influence many operators, including myself, not to be conservative with benign tumors in women past the age of thirty-nine except in the unusual instance in which the desire for pregnancy is of paramount importance.

As regards the malignancies, I believe that our management should be uncompromising, that it should consist of removing uterus, tubes and ovaries when possible, regardless of the patient's age, of resecting contiguous structures when such resection appears worthwhile, and of giving x-radiation. As in every phase of medicine, there are exceptions to sweeping statements. We know of long-term survivals after nothing more than unilateral oophorectomy. Some of these patients had had just tiny cancers inside otherwise benign serous or mucinous cysts. I know of a woman who is well fifteen years after nothing more than an ovarian resection. There have been gratifying lengths of survival in patients with metastases who had not received x-ray therapy. However, these are, indeed, just exceptions—due to luck and the way the cancers happened to behave.

In connection with unexpectedly good outcomes, the following figures are based on results at the Free Hospital for Women: One hundred twenty-four (52 per cent) of those with ovarian malignancies had obvious metastases at the time of surgery. Of these women, fourteen (11.3 per cent) were well without evidences of disease at five to fifteen years, and thirteen (10.5 per cent) lived from five to thirteen years before they succumbed. Although tumor biology undoubtedly played a part, I attribute most of this salvage to x-radiation. Reported figures are unanimous that the percentages of five- and ten-year survival are higher by 5 to 18 points among those who had received x-ray therapy. I think we can anticipate improved salvage through refinements of radiation and in the use of chemotherapy. There will still be radioresistant cancers, however, and it is in patients with these that we can attempt to eke out a few more survivors by "later look" surgery.

"LATER LOOK" SURGERY

Because distant metastases are the usual accompaniment of locally recurring ovarian cancer, experience with "later look" surgery is necessarily limited and likely to be disappointing. My small experience with four patients, three of whom are now well, began in 1945.

Mrs. M. L. A. (No. 18012), in December, 1942, underwent complete hysterectomy with bilateral salpingo-oophorectomy at the age of fifty-eight. A 16 cm. papillary cystadenocarcinoma, which had burrowed retroperitoneally and extended above the pelvic brim, mostly on the right, was dissected out without rupture. Radiation therapy was given postoperatively. In October, 1944, further radiation was given for an 8-cm. mass in the right pelvis. The mass remained unchanged. Since the patient was well in other respects, surgery was undertaken again in June, 1945. There being no evidence of distant spread, the mass and some ileum which it had invaded were widely excised. Under the microscope the cancer appeared to have been unaffected by x-radiation. The patient is now well nearly twelve years after this second procedure.

One may well inquire why the recurrence was treated with x-rays when it had already demonstrated radioresistance. At the time I was thinking only of palliation, assuming that the recurrence implied a hopeless situation. Besides, radiation may trap these cancers by its effects on surrounding tissues. Next, one may well ask why I waited nearly eight months before taking the second look. It simply took me that long to realize that this cancer preferred to remain locally invasive; furthermore, an adjustment of perspective is required when one undertakes "later look" surgery. On a small chance that the result will be gratifying, it means exposing a patient whose life span is likely already to be limited to morbidity and the possibility of earlier death. That chance

has become more often justifiable only in the past fifteen years with the assurance given by modern surgical management.

When Mrs. L. S. M. (No. 37407), aged fifty-one, came to me in April, 1948, she said she had undergone three operations for a tumor which "comes back," the first procedure consisting of hysterectomy and bilateral salpingo-oophorectomy four years previously. There had been no radiation therapy. She felt pretty well but did have complaints referable to a 5 inch cystic mass extending into the lower left part of the abdomen from the pelvis. Later microscopic study confirmed the clinical impression of rectal, vesical and vaginal involvement by a mucinous cystadenocarcinoma. Examinations by x-rays revealed no metastases. The left kidney was functionless; there was some ureteral obstruction on the right.

The patient was given x-ray therapy and prepared for radical surgery. No metastases were encountered while the omentum and small bowel were being freed from their extensive adhesions and while everything was being examined above the pelvis. Exenteration was performed, leaving her with a right cutaneous ureterostomy, a high sigmoid colostomy and no iliac venous return at all on the left. The left ureter was divided and its atrophied kidney has remained quiescent.

After six months the left lower extremity gave the patient no more trouble. Her main problem, of course, has been recurrent right renal infection. She has become adept at preventing this by an adequate intake of fluid and the timely institution of sulfonamide therapy. At the end of her ninth postoperative year she continues to be reasonably healthy and happy, without evidence of recurrence.

No one these days would, I believe, elect to perform pelvic exenteration as a primary procedure for ovarian malignancy, but this case stimulated me to be on the lookout for patients in whom it might be done once a cancer shall have demonstrated its predilection for remaining in the pelvis. I think I failed in the next case because I did not become aware soon enough that the cancer was not of the distantly metastasizing variety and I did not perform exenteration at the second look.

Mrs. M. C. (No. 43410), aged fifty-one, had her primary surgery and x-radiation in September and October, 1950. In November, 1951, the sigmoid and its mesentery were widely and deeply removed because of persistent papillary cystadenocarcinoma. This is the time when I believe I should have performed exenteration, for at the next exploration in July, 1953, the cancer was in the right upper pelvis and had involved cecum and terminal ileum. These were excised and exenteration was performed. No tumor was found in the deep pelvis or bladder region. Thereafter the cancer grew rapidly but still seemed to remain below the level of the umbilicus. The patient died in April, 1954.

Mrs. M. L. D. (No. 53375), aged thirty-seven at the time, underwent supravaginal hysterectomy with coring out of the cervix, bilateral salpingo-oophorectomy and resection of the omentum in December, 1951, because of bilateral papillary serous cystadenocarcinoma with an omental metastasis. There were proved metastases in the pouch of Douglas. Radiation therapy followed. The patient was referred to me in February, 1935, because of a 4-cm. mass behind the cervical stump. This was treated with radium locally and a second course of x-rays. I wonder now why I did not operate; but although she was feeling well and there was no evidence of metastasis, I was influenced by the significance of the previous omental disease.

Radiation proctitis, then a rectovaginal fistula, ensued. In December, 1953, abdominal perineal resection was performed and included excision of the cervix, upper vagina and broad ligaments and bilateral pelvic lymphadenectomy. There were no distant metastases; the nodes and the lines of excision were free of disease, but viable tumor infiltrated cervix, vagina and rectum. At this point the prognosis appeared promising except for the likelihood of further radiation complications.

All seemed well until the appearance of bloody discharge through the vaginal stump in August, 1954. The previously healed stump had opened, and where it impinged on the sacrum we found highly anaplastic, undifferentiated carcinoma. Presumably it was dedifferentiated ovarian recurrence. Within a week small bowel content began to drain through the vagina. Despite this combination of cancer, radiation damage and a fistula of the small bowel resulting from one or the other, the patient felt well and was without evidence of extrapelvic disease.

It seemed that immediate surgery might unavoidably spread this ugly cancer; that first an attempt should be made to destroy it. Diathermy coagulation of the tumor-fistula area was considered too limited in its scope. Therefore in September, 1954, a necrotizing dose of radium was applied and in October surgery was performed. The terminal ileum, with its fistula, and the cecum were densely adherent in the pelvis. They were resected; the bladder and vagina were removed; and the lower sacrum, where there had been tumor, was charred with diathermy. An ileal bladder was constructed. To keep intestine out of the pelvis, a ball of gauze wrapped in a thin sheet of polyethylene

was placed in such a way that it could be removed later from below. No evidence of cancer was found above the pelvis and no tumor was seen on microscopic examination of the excised tissues.

The patient did well following this third look and is now well two and a half years later and five and a third years from the first operation. A fourth look was necessitated in February, 1955, because of acute intestinal obstruction, but there was no sign of recurrence.

The failure of ovarian cancers to make their presence known early in their growth and the fact that over half of them have metastasized by the time they are discovered, are unhappy facts concerning these lesions. A 22 per cent salvage with radiation in 124 cases in which these were metastases is therefore an unexpectedly good outcome. Similarly, my small and perhaps unique experience with "later look" surgery in radioresistant cancers of the locally invasive variety may also be considered, thus far, unexpectedly good.

DISCUSSION

JOHN J. BYRNE (Boston, Mass.): I am sure that Dr. Smith would be happy to answer any questions that might be raised by this thought-provoking discussion. I think it is interesting the way the pendulum seems to swing back and forth. There was a time when we used to take out the ovaries at the time of hysterectomy. Then, due to all the metabolic changes which might ensue, we were warned not to remove them. And now we hear again that it might not be such a bad idea in selected cases. I wonder if Dr. Smith might be a little bit more specific on that point. Do you mean you really believe that at every abdominal hysterectomy we should remove the ovaries, or should we look at them and try to form some idea as to what is wrong?

DR. SMITH: I would specifically say that when we perform an abdominal hysterectomy, and perhaps now a vaginal hysterectomy, in patients *after the age of thirty-nine*, we had better not keep the ovaries in except when conservation is demanded by the patient. Before the age of forty, of course, it is a matter of conservation in relation to the general belief of so many people that the ovaries have a function which ought to be maintained as long as possible. On the other hand, many believe that, after all, patients can do very well with substitutive estrogen therapy and therefore perceive no need of ovarian conservation at the time of hysterectomy.

DR. BYRNE: Any other questions?

QUESTION: Do you believe, Dr. Smith, that the removal of a primary ovarian tumor will change the growth of the metastases?

DR. SMITH: It is hard to be dogmatic about that. We have all had the impression that following the removal of the primary tumor the growth of the metastases may be slowed down. But I do not know how this can be proved.

QUESTION: Have you had any chance to compare the incidence of carcinoma of the breast in patients who have had ovaries removed with that in the general female population?

DR. SMITH: I am sorry to say that that has not been done on a large scale. However, twenty years ago Herrell reported figures from the Mayo Clinic indicating a decreased incidence of carcinoma of the breast in ovariectomized women.

Diagnosis and Treatment of Tumors of the Testis

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TUMORS of the testis comprise a small group so far as all malignant lesions affecting the male are concerned (about 1 per cent), yet their early treatment is very important as nearly all are lethal unless treated and most patients so afflicted are young. Early diagnosis must still be stressed because at the present time there is very often a delay of several months between the recognition by the patient of a testicular abnormality and definitive therapy. Sometimes this is due to reluctance on the part of the patient to seek medical aid but much too often the physician fails to recognize the testicular swelling for what it is. Delay in early recognition and orchiectomy may cost the patient his life as the dissemination of tumor cells in all cases is a function, even though unpredictable, of time.

Testicular tumors are always most interesting to pathologists because of the microscopic patterns encountered in the tumors and the wide variety of metastatic lesions secondary to embryonal and teratomatous lesions. To the urologist the diagnosis and treatment of testicular tumors is a challenge. Therapy is not yet standardized. We do not yet know with certainty what the best therapy may be in each case—what the limitations of surgery are, what deep radiation therapy may be expected to accomplish in each instance and how much therapy should be given. Little has been done in application of chemical or hormone therapy for testicular tumor.

Campbell [1] states that from 1935 to 1946 there were 37,963 individual cases of cancer occurring in Connecticut, a state of 1,750,000 inhabitants. Of these, 185 were tumors of the testis, epididymis and spermatic cord, an incidence of two per each 100,000 males. These tumors constituted 0.5 per cent of all cancers in both sexes and 1.1 per cent of all cancers in males. Lewis [2] estimates that the incidence of testicular tumor is probably less than one in 50,000 males per year. During the Second World War [3] 922 testicular tumors which developed among men in the Armed Forces were examined at the Walter Reed Army Hospital or by the Army Institute of Pathology. Although tumors of the testis occur in infants and older age groups, the mean age at onset is about thirty years. (The average age for seminoma is given by Lewis as thirty-one and for all other tumors of the testis as twenty-six.) Similar findings have been observed by other writers.

The right testis is affected by tumor more frequently than the left. It has been suggested that perhaps this reflects the greater instance of cryptorchidism on the right side. Experience appears to have established the fact that undescended testes or testes which have been brought to the scrotum by operative procedures exhibit a higher incidence of tumor than normal testes. This is illustrated by the fact that in most series of testicular tumors up to 15 per cent occurred in undescended or maldescended testes or testes previously brought into the scrotum.

The actual cause of tumor of the testis remains completely unknown. The etiological significance of trauma has not been established. At the present time, therefore, aside from the possible desirability of removing an ectopic or undescended testis, nothing else in the way of preventative therapy can be suggested.

PATHOLOGY

In order to interpret the clinical and pathological features of testicular tumors, some sort

of an explanation of their origin and development must be considered. Furthermore, a pathological classification based on microscopic characteristics and clinical behavior is necessary if treatment is to become standardized and the results of therapy comparable.

There are metastatic tumors of the testis, but most arise from the component cellular elements of the testis itself. Primary tumors of the testis may be divided into three groups: (1) those arising from the germ cells; (2) those arising from the cells of Leydig (interstitial cell tumors); and (3) those arising from connective tissue cells (Sertoli cell tumors, fibromas, lipomas, hemangiomas, etc.). Tumors arising from germ cells comprise about 95 per cent of the total.

Tumors arising from germ cells can be divided into two main groups. These are: (1) tumors which exhibit one type of cell, both in the primary and metastatic lesion—the unicellular seminoma; and (2) tumors which simulate in a distorted fashion the development of an embryo. In 1906 Chevassu [4] wrote, "For the explanation of formations as complex as the teratomas, one cannot but recognize a mode of development, analogous to that which takes place in the development of the embryo."

There is no difficulty in explaining the development of malignant potential in a germ cell or cells which in the process of tumor formation produce tissues which simulate the development of an embryo. Seminoma has been, by virtue of its unicellular characteristic, difficult to fit into this concept. Chevassu suggested that seminoma is a tumor arising from a spermatoblast. Ewing [5] believed that all germ cell tumors of the testis were teratomas and that seminoma was a one-sided development of a teratoma in which other elements were overgrown and disappeared. He summarized his views on this as follows: "1–the characteristic structure is often seen in teratomas, adult or embryoid; 2–in a very early embryonal carcinoma (seminoma) I found minute traces of cartilage, endodermal and alveoli, and squamous epithelial groups; 3–the rapid growth of the malignant embryonal elements gives unusually favorable opportunity for the overgrowth and suppression of other elements; 4–the only known tumor of the adult spermatoblast is very different from the seminoma. Barring the possibility of an unrecognized form of metaplasia, the teratomatous relation of our tumor (seminoma) seems to be demonstrated. It remains possible that the seminoma may arise from spermatoblasts incited to growth by the presence of a teratoma."

More recently, Melicow [6] has stated that, "The family of germinal tumors is comprised of 2 sub groups because of differences in the response of the original germ cell to some unknown carcinogenic agent (S) or factor (S). The response varies as follows: A. When the germ cells are stimulated to divide and multiply but at the same time *retain* their trigerminal potential and maintain the original appearance, the result of tumor is a unicellular mass known as seminoma. B. When the carcinogenic agent (S) or factor (S) not only stimulates the cells to divide but at the same time also forces them to *release* the trigerminal potential inherent in their nuclei (this without benefit of union with an ovocyte), then a chain of events is set in motion which simulates the development of an embryo. The resulting masses comprise the embryomatous and the teratomatous tumors."

At present it can only be stated that the explanation of the development of the unicellular seminoma is not known. It is apparent, however, that the cells comprising this tumor have characteristics suggesting direct origin from the germ cell or a closely related cell, perhaps the spermatocyte. One characteristic is their extreme radiosensitivity.

In 1951 my thoughts on the development of germinal tumors of the testes were expressed as follows [7]:

"In the testis the normal process of division of the primitive germ cell is to reproduce in kind and to divide repeatedly to form cells which are termed spermatocytes, sometimes called spermatocytes I. So far as is known there is no intermediate cell type. Each spermatocyte is capable of producing only four descendants. Each undergoes a maturation process characterized by division into two cells called spermatocytes II during which the chromosome content of the nucleus is divided in half. Each spermatocyte II divides again to form two spermatids which become transformed into spermatozoa in some manner while in relation to the Sertoli cells. Spermatids appear to be incapable of division.

"Observations concerning the development of testis tumors necessitate the assumption that a single or several primitive germ cells or

spermatocytes of the first order, which are obviously totipotent as well as the original germ cell, undergo transformation so that instead of developing normally to the spermatid stage, benign or malignant teratomas result.

"Simple stimulus to abnormal growth of a single germ cell would appear to result in a so-called adult teratoma which is characterized by the presence of adult tissues derived from the various germ layers, though not necessarily including representative tissue from each. Such tumors are not themselves generally malignant, though metastasis and death occasionally occur. One must assume in these instances that the tumor is actually not an adult teratoma, or that malignancy developed in the tissues of the teratoma itself rather than as the result of an original attribute of the germ cell which underwent abnormal division. The process of early development of an adult teratoma has not been observed so far as the writers know, but it must be assumed that the germ cell stimulated to abnormal growth divides in a manner similar to the fertilized ovum to form first a morula-like stage consisting of a small mass of cells which even then are differentiated as to potentialities, some to form ectoderm, others endoderm, mesoderm, and still others trophectoderm. Trophectoderm must either be overgrown, atrophic, or dormant for long periods. When death occurs due to metastasis, chorio-epithelioma is usually the cause. Whether something resembling the blastula stage of the embryo with further differentiation of cells is formed is not known. In any case, cells with certain potentialities develop and differentiate to form recognizable structures derived from one or more of the germ layers.

"Malignant testis tumors appear to arise from a germ cell transformed in some fashion to a malignant cell. The malignant quality is transmitted to all its progeny even though the ability of the cell to develop through imperfect morula or blastula stages into one or more of the primitive germ layers is presumably retained. In some instances testis tumors consist of carcinoma derived directly from one of the primitive germ layers including trophectoderm without differentiation into further complex tissues. Such tumors are illustrated by those called embryonal carcinoma by Friedman and Moore and adenocarcinoma and trophocarcinoma by Lewis. In other types, such as the teratocarcinoma of Friedman and Moore, some of the cells differentiate into ectoderm, endoderm, mesoderm, or trophectoderm forming recognizable teratomatous growths in conjunction with less differentiated types of carcinoma derived from primitive germ layers. Individual cells form differentiated metastases in situ, which appear different, not recognized, or long since overgrown in the primary lesions. This presumably accounts for the great variation in metastases and the presence of differentiated metastases such as chorio-epithelioma and various types of carcinoma or organoid structures not noted in the primary tumor.

"It is not known with certainty whether a single malignant germ cell sometimes divides to form other similar malignant germ cells of similar capabilities (primitive germ cell carcinoma), thus giving rise to multiple cells from each of which teratomatous growths may arise (multicentric origin) or whether usually a single malignant germ cell develops through a morula or blastula-like stage. From these obviously differentiated cells, carcinoma of various types, or teratomatous growths develop, depending on which cell types grow fastest and obscure or destroy other early structures.

"That there may be at times division of the original malignant primitive germ cell to form other malignant germ cells is suggested by the observations of Lewis and earlier writers. He noted four tumors termed embryomas in which the primitive embryonic tissue formed bodies resembling blastocysts (imperfect blastula formations) which he felt could be regarded as imperfect embryos. 'The cells were not completely differentiated, but the picture of a signet ring body of primitive ectoderm, with an eccentric cavity lined by thin endodermal cells, suggests an attempt to form an embryo.' In one case, bodies resembling blastocysts were found in retroperitoneal metastatic nodes. These observations suggest the presence of and metastasis of primitive germ cells or cells slightly more differentiated than the original malignant cell type.

"Seminoma cells themselves seem incapable of further differentiation since metastases of this tumor are similar in cell type. On the other hand, areas of seminoma are noted in conjunction with teratomatous lesions and may be present either in the original or metastatic lesion. This suggests to the writers that this tumor is derived from cells other than primary

germ cells and that actually the cells are completely differentiated as to type, whatever this may be. When found in mixed tumors the areas must differentiate in situ from a more primitive cell. These assumptions might not allow seminomas to be classed as one-sided

TABLE 1
COMPARATIVE CLASSIFICATIONS OF TESTIS TUMORS OF GERM CELL ORIGIN

Friedman and Moore	Lewis
A. Seminoma	A. Seminoma
B. Embryonal carcinoma	B. Adenocarcinoma
B_1. Chorioepithelioma	1. Undifferentiated embryonal
C. Teratocarcinoma	2. Embryonal
D. Teratoma	3. Embryonal papillary
	C. Trophocarcinoma
	1. Cytotrophoblastoma
	2. Choriopapillary adenocarcinoma
	3. Chorioepithelioma
	D. Immature teratoma with elements of A, B or C.
	E. Mature teratoma with or without elements of A, B or C.

teratomatous growths even though they may develop in teratomas."

Chevassu, Ewing and Hinman suggested pathological classifications for germ cell tumors of the testis which gave rise to considerable controversy, and it was not until 1946 that Friedman and Moore [3], following careful study of 922 tumors of the testis encountered at the Walter Reed Hospital and the Army Institute of Pathology during the last war, suggested a rather simple classification. This has been generally accepted and forms the basis for most discussions of testicular tumor at the present time. Their studies showed that only four fundamental structural patterns were encountered, alone or in combination, in the vast majority of tumors. Of the 922 tumors, over 96 per cent fell into one of these categories, 1 per cent were interstitial cell tumors and 3 per cent were rare or unclassifiable varieties.

Lewis has advocated a more complicated classification which has the advantage of providing more specific grouping of embryonal tumors. Table 1 shows the classification of Friedman and Moore and also that of Lewis for comparison. It should be noted that Friedman and Moore include under embryonal carcinoma all of the embryonal tumors arising from embryonal ectoderm, endoderm, mesoderm and trophectoderm, except choriocarcinoma, whereas Lewis separates tumors containing trophectoderm or its derivatives from the other embryonal tumors. This may serve a useful purpose inasmuch as tumors with trophectodermal constituents have in general a poorer prognosis than tumors without this cellular content. Melicow has recently submitted a classification which is essentially the same, although it has a somewhat different emphasis. At the Massachusetts General Hospital we follow Friedman's and Moore's classification.

A pathological classification of testicular tumors is difficult because in any given tumor there may be a great variety of cellular components even though a large part of the tumor may show fairly uniform composition. In order to be certain of the classification of any given tumor, one must serially section the entire tumor and examine well nigh all of the tissue microscopically. This is, of course, impractical. In practice one makes blocks at random including areas of tumor which appear grossly different. Our inability to study all tumors of the testis completely probably accounts for the occasional mistakes made in evaluating tumors. For instance, although most of the lesion may be seminoma, foci of embryonal cells or teratocarcinoma may be missed. This might lead to inadequate therapy if these elements have metastasized since they are not usually radiosensitive, at least not to the same degree that seminoma cells are.

SEMINOMA

These tumors comprise from 40 to 50 per cent of all tumors of the testis. The average age of patients is about thirty years. However, seminoma is the testicular tumor usually found in older men. Its appearance on cut section is that of a solid white or pinkish tumor. Microscopic sections reveal, as indicated in Figure 1, masses of fairly large oval cells with prominent, deep-staining nuclei. Connective tissue trabeculae are seen and lymphoid stroma is often noted. Testicular tissue about the margin of the tumor is compressed and invaded to some extent. There is considerable variation in seminomas. Some are composed of rather uni-

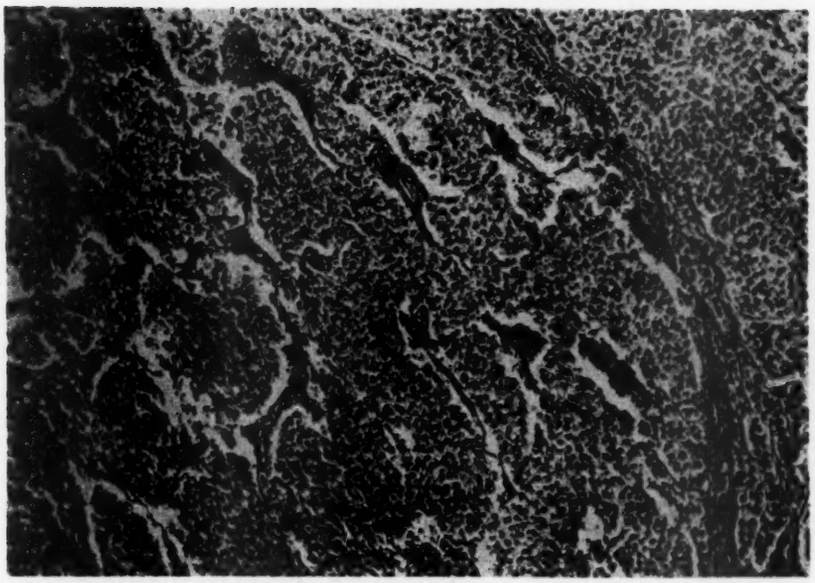


FIG. 1. Seminoma of testis. Rather typical seminoma with lymphoid infiltration. Note uniform cellular structure.

form cells and nuclear content while others appear more anaplastic with considerable variation in cellular size and nuclear content. In more anaplastic tumors the stroma is less evident and lymphoid tissue may be lacking.

Seminomas generally metastasize first to the retroperitoneal glands on the side of the tumor with subsequent extension probably by way of the thoracic duct to the lungs and other organs. Visceral metastasis may be present occasionally without involvement of the lymph glands. Tumor cells are very radiosensitive so that 1,500 r are usually sufficient to kill all cells. In practice we accept 2,000 r as the proper tumorcidal dose. Because of their extreme radiosensitivity, surgery after orchiectomy for diagnosis is rarely necessary or desirable. It has been stated that metastases from seminomas may be different in microscopic appearance (embryonal or teratocarcinoma) but I have never encountered this. The explanation of this observation, it would seem to me, is that error was made in diagnosis of the original lesion probably because of incomplete microscopic examination of the primary tumor. Areas of seminoma are not infrequently encountered in both embryonal carcinoma and teratocarcinoma, and seminoma may be the only metastatic lesion in a few cases. Seminoma may be confused with lymphosarcoma or reticulum cell sarcoma. This is quite important because the ultimate prognosis of lymphosarcoma and reticulum cell sarcoma is hopeless whereas that of seminoma may be very good.

EMBRYONAL CARCINOMA

These tumors comprise somewhat more than 20 per cent of all testicular tumors. The age of patients at onset is younger than for seminoma. Lewis gives an average age of twenty-six years for all patients with tumors other than seminoma. Embryonal carcinomas are irregular, firm, and often tender. Cut section shows irregular masses of firm, pinkish tissue often with areas of old or recent hemorrhage. Microscopic study shows great variation in cellular content and arrangement. Very few tumors are microscopically identical. Tissue patterns vary from blastula-like structures lying in an actively growing stroma (the embryoma) to solid masses of deep-staining cells sometimes with the syncytial characteristic of tissue derived from trophectoderm. The underlying structure often suggests endodermal origin. A common microscopic pattern is illustrated in Figure 2.

These lesions metastasize both by retroperitoneal lymph nodes and, when choriocarcinomatous elements are present, by way of vascular channels. Any tumor with demonstrable choriocarcinoma therefore has a poorer prognosis than with embryonal tumors. Some lesions are quite radiosensitive, even as sensitive as seminoma. Others are quite radioresistant so that when distant metastases are

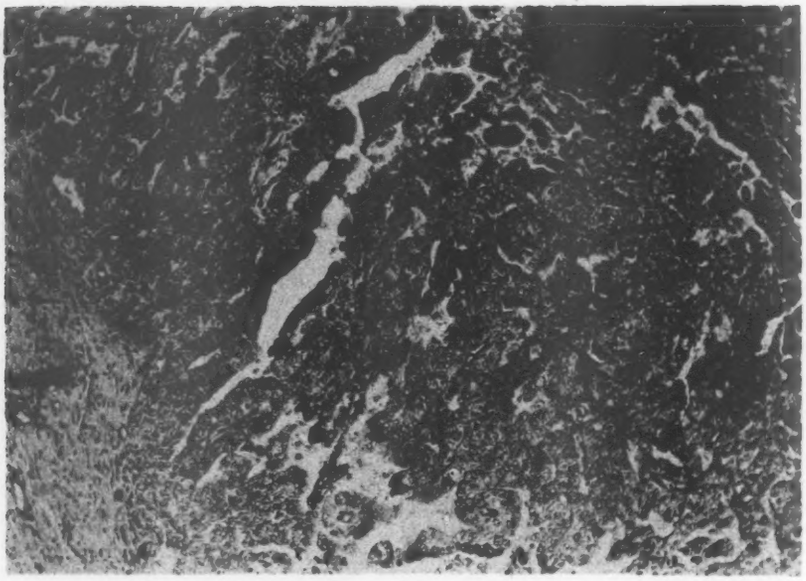


FIG. 2. Embryonal carcinoma of testis. This illustrates a common microscopic pattern seen in embryonal cell cancers.

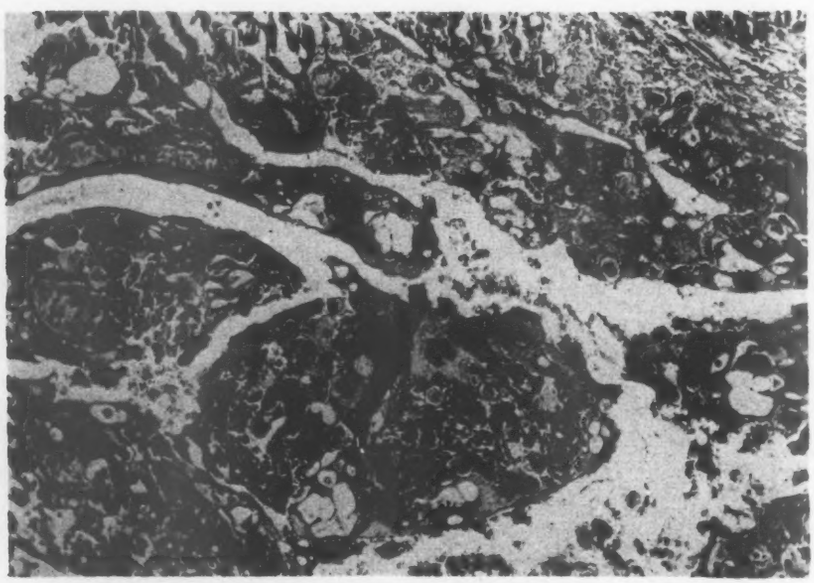


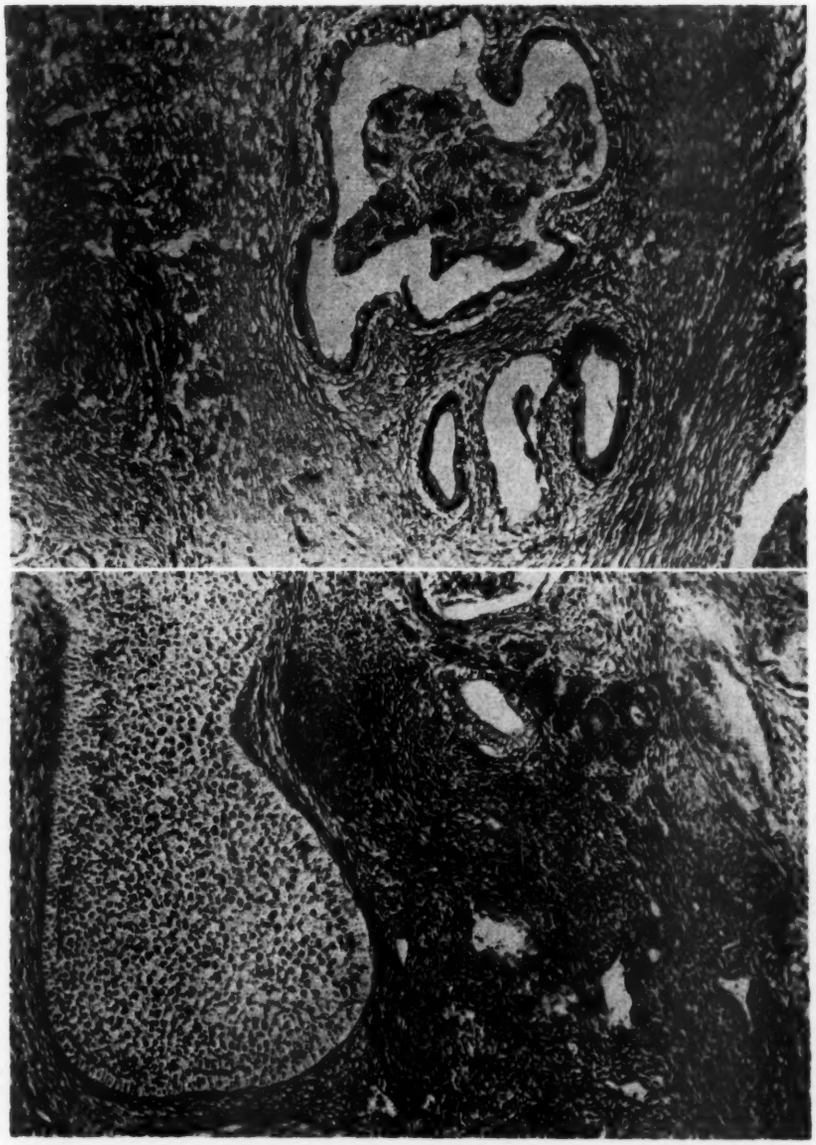
FIG. 3. Choriocarcinoma of testis. Note multinucleated cells.

not demonstrated dissection of the retroperitoneal gland on the side of the lesion is indicated. Four thousand r are necessary to provide any chance of cure if deep roentgen therapy is to be used.

Pure choriocarcinoma of the testis (Fig. 3) is fortunately quite rare, constituting only about 1 to 2 per cent of all testicular tumors. Because of the tendency of this tumor to early invasion of the blood vessels, the outcome is considered completely hopeless and orchiectomy for diagnosis is all that is indicated.

TERATOMA AND TERATOCARCINOMA

Teratocarcinomas and adult teratomas constitute about 30 per cent of all testicular tumors. I prefer to classify these together because it is extremely difficult to be certain that an adult teratoma, so called, does not contain foci of teratocarcinoma. These tumors



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FIGS. 4 and 5. Teratocarcinoma of testis. Cell groups suggestive of intestinal glands are very common as illustrated in both microscopic sections. Any type of tissue may be found.

are usually nodular, firm and relatively non-tender. On cut section they show firm areas interspersed with cysts, cystic areas or areas of hemorrhage. A microscopic characteristic is the presence of tissue clearly differentiated into glands, epithelial masses, often with keratinization, cartilage or nervous elements set in a loose or dense stroma of obvious mesodermal origin. Areas of seminoma, embryonal carcinoma, with cells of chorionic origin may be noted. Metastases may contain any of the component cellular elements. Adult teratoma is a tumor in which complete differentiation of all embryonal elements has occurred. This is very difficult to determine with certainty even if most of the tumor can be examined microscopically, and our own experience indicates that all so-called adult teratomas should be treated as if malignant areas were present. Figures 4 and 5 show representative areas of teratocarcinoma.

Teratocarcinomas metastasize initially in most instances by way of lymphatics to the retroperitoneal glands but blood-borne metastasis may occur, particularly if choriocarcinomatous elements are present. Dissection of the

retroperitoneal gland seems particularly indicated after the diagnosis of teratocarcinoma since the presence of differentiated malignant tumor poses a real problem so far as deep roentgen therapy is concerned. These tissues are extremely radioresistant, perhaps as resistant as normal tissue.

METASTASIS

Metastasis from testicular tumors, other than choriocarcinoma, generally occurs initially to the retroperitoneal lymph nodes. Early metastasis to the lymph nodes from right-sided tumors are most often found in the pericaval glands between the point where the right spermatic vein enters the cava and the renal pedicle. Left-sided lesions metastasize early to glands at the level of the renal pedicle. However, since the lymph drainage from the epididymis and the scrotum is to the inguinal or external iliac glands, when the tumor is large and involves the peritesticular structures one must look for metastatic disease in the inguinal or deep pelvic lymph nodes. Occasionally, due to the extensive lymphatic network in the retroperitoneum, primary lymph gland metastasis may be on the opposite side, left-sided lesions involving the pericaval nodes, or right-sided lesions involving the periaortic nodes. Supraclavicular and mediastinal glands are frequently involved secondarily. Blood-borne metastasis may arise by way of dissemination of cells through the thoracic ducts or by way of direct invasion of the blood vessels. The lung and liver are the most frequent sites of metastasis but any organ may be involved. These pathological characteristics, which are by no means exhaustively described, constitute the basis for planned therapy.

SYMPTOMS

There are no early symptoms of testicular tumor other than changes of size and consistency of the organ. Occasionally there may be an ache in the testicle or groin. Tumors of the testis metastasize occasionally before the primary tumor is noted by the patient from lesions so small that they may not be palpable even by a skillful physician. When this occurs symptoms will depend on the location of metastases. If the retroperitoneal glands are involved there may be a lumbar ache on the side of the tumor. If metastasis to the supraclavicular nodes occurs, attention may be drawn to the development of a mass in this area. Occasionally, there may be primary pulmonary symptoms due to mediastinal or lung metastases. Every now and then enlargement of the breasts may be a presenting symptom. This occurrence is due to either hormonal elaboration by the tumor or to secondary alterations in pituitary function.

Tumors developing in intra-abdominal testes are usually recognized very late. These may become evident by an enlarging lower abdominal mass or because of an acute abdominal episode occasioned by rupture of the tumor. The first symptom in one of our cases of intra-abdominal testicular tumor was rectal tenesmus and bleeding because of actual invasion of the rectal wall. Tumors developing in testes located in the inguinal canal or in an ectopic position in relation to the external inguinal ring are usually noted earlier, probably because the swelling is more likely to be felt or the enlarging testicle traumatized.

DIAGNOSIS

To avoid delay in the diagnosis of testicular tumors, any scrotal enlargement must be examined carefully. Unfortunately, one of the greatest problems we face is not the patient's failure to present himself to a physician reasonably early but rather the failure of the physician to evaluate findings promptly. Some swellings are erroneously diagnosed as hydroceles, others as epididymitis and occasionally hematoceles if a history of trauma is given; now and then reasonably obvious tumors are dismissed as of no consequence. A physician should consider each scrotal swelling a possible testicular tumor until proved otherwise. The differential diagnosis must, of course, include hydrocele, epididymitis, torsion, trauma and tumor.

Because hydroceles are not infrequently present in association with testicular tumors they should be carefully aspirated without puncturing the tunica albuginea of the testis. Usually the fluid is clear and straw-colored. If it is bloody, particularly if dark or black, it suggests tumor invading the epididymis or the testicular tunics. The testis should be carefully palpated after the fluid is withdrawn. If it is found to be nodular, firm or heavy, the testis almost certainly contains tumor.

Epididymitis is usually obvious because of pain, fever and tender enlargement of the

epididymis. Perhaps the first point to be considered when examining a scrotal swelling is whether it involves the testis or epididymis. Tuberculous epididymitis is rarely very tender and is very firm and nodular. Epididymal cancer is rare but must be considered when a firm, non-tender swelling of the epididymis is present. If the testis alone is enlarged, firm and heavy, a testicular tumor is certainly present. A gumma may not be distinguishable from a tumor of the testis by palpation but rarely comes up for differential diagnosis these days. Small intratesticular neoplasms may be difficult to diagnose but should be suspected if normal testicular consistency is lost.

One should neither take a biopsy of a testis through a scrotal incision nor insert needles into the tumor since this destroys the natural barriers about the tumor and allows fungation of tumor into the tunica vaginalis or scrotal tissues. If a diagnosis cannot be made by external examination, an inguinal incision should be made, the inguinal canal opened, the spermatic cord freed and the cord occluded with a rubber-shod clamp at the internal inguinal ring. The testis then should be gently freed from the scrotum together with its tunics, the tunics incised and the testicle inspected. Usually a diagnosis can be made by palpation and inspection of the testis, but if it cannot be made with certainty it is probably better to remove the testicle than to incise and examine the lesion. This may be necessary occasionally and should be carried out only after carefully packing off the wound to prevent the implantation of cells.

When a testicular tumor is found or suspected, the inguinal, iliac and supraclavicular gland areas should be carefully palpated in an effort to determine whether superficial glands are involved. Retroperitoneal masses can be palpated if the metastatic masses are large, but smaller lesions are rarely palpable. Roentgenograms of the chest and intravenous urograms should be taken in every case to determine the presence or absence of pulmonary or mediastinal metastases and to delineate the position of the kidneys and ureters which may be displaced or distorted by the presence of metastatic disease in the retroperitoneal glands. Early metastasis to the retroperitoneal gland may be demonstrated by the medial or lateral crescentic displacement of a segment of the ureter. Breasts should be examined for evidence of gynecomastia which is present not infrequently. It is thought to indicate the presence of tumors of trophoblastic content although this is not invariably the case. A twenty-four-hour urine specimen should be quantitatively tested for urinary follicle-stimulating hormones and chorionic gonadotropic hormones. This is of great value because if strongly positive, particularly so far as the gonadotropic portion is concerned, it indicates the presence of trophoblastic tissue; and repeated tests after orchiectomy, dissection of the retroperitoneal gland or deep roentgen therapy may be of great aid in determining the effectiveness of therapy or the spread of metastatic disease.

TREATMENT

The plan of treatment for testicular tumors depends on (1) the pathological nature of the individual tumor, (2) the probable presence or absence of metastases to the retroperitoneal lymph gland, (3) if demonstrably present, how large or extensive and (4) the presence or absence of distant metastases to the supraclavicular or mediastinal nodes, the lungs, liver, bones, etc.

Prompt orchiectomy, as outlined previously, to determine the nature of the tumor regardless of the presence or absence of metastases is necessary. Because one may occasionally be dealing with choriocarcinoma I believe this should be regarded as an urgent matter. Furthermore, I have in selected cases performed dissection of the pelvic lymph nodes through an elongated inguinal incison at the time of orchiectomy, for two reasons. The first is to allow ligation of the spermatic cord at a high level, and the second is to accomplish easier and more complete dissection of pelvic lymph nodes than is afforded by the approach to lymph nodes about the pelvic brim. Inguinal nodes would be included if involvement of the epididymis or scrotum was found. Of course, if seminoma is found to be present this is unnecessary, although it may establish the presence of metastasis and the absolute need for further therapy.

After microscopic diagnosis has been made, one is in a position to plan further therapy. If seminoma is found, our plan is to administer deep roentgen therapy to the pelvic lymphatic areas on the side of the tumor and to the retroperitoneal gland areas through anterior and posterior ports for a total of 2,000 r

tissue dose. If metastatic disease to the supraclavicular glands, the mediastinum or the lungs is demonstrated, these areas are treated also. Occasionally, if the patient tolerates abdominal radiation well, even though metastatic disease has not been demonstrated above the diaphragm, prophylactic radiation has been given to the supraclavicular and mediastinal areas. If this is not done prophylactically and metastases to these areas subsequently appear, treatment is given as indicated or as possible. It would appear on the basis of our experience and from reports in the literature that seminoma can be controlled in all patients without widespread metastatic disease. This implies that metastatic disease to the retroperitoneal glands can usually be controlled, but that if dealing with multiple areas of metastasis, one may not be able to give treatment fast enough to control all areas. Lewis recently reported a five-year survival of 85 per cent of patients with seminoma treated at the Walter Reed Hospital. Our experience indicates that this is possible to attain.

If embryonal carcinoma or teratocarcinoma is found in the absence of demonstrable metastasis above the diaphragm and in the retroperitoneal glands, or if retroperitoneal disease is present and judged operable, radical dissection of the retroperitoneal glands is performed on the side of the primary lesion. For this we prefer the thoracoabdominal incision performed by resecting the tenth rib and extending the incision downward across the abdomen toward the pubic spine. The Nagamatsu incision is probably equally good. All of the perineal fascia and fat and all the tissues from about the aorta and the cava and between the cava and aorta, depending on the side operated upon, are carefully resected from the crus of the diaphragm to the femoral canal. This resection is shorter and considerably easier if the pelvic portion of the dissection has been performed, previously. If many positive glands are present or if one can palpate enlarged glands on the opposite side, a similar operation is performed after a suitable interval on the side opposite the tumor. No death or serious complication has occurred in twenty-eight consecutive operations I performed during the last nine years.

Furthermore, in the group of patients in which the dissection was not performed bilaterally, only in one patient thus far has metastatic disease developed on the contralateral side in the presence of negative nodes on the side of the tumor.

When no positive glands have been found, deep roentgen therapy has not been given. When positive glands have been removed, deep roentgen therapy has generally been employed after operation in the hope that microscopic disease which remained might be destroyed. In any case, one wishes to provide everything possible in the way of therapy; if x-ray therapy is given carefully there seems to be no contraindication when used in doses up to 4,000 r.

Other patients with inoperable disease have been given deep roentgen therapy in the hope that the lesions might respond, although to date, with the exception of two patients with embryonal carcinoma and one with teratocarcinoma, none have survived.

Seventeen patients with teratocarcinoma and five with embryonal carcinoma have been operated upon. Three of these, each of whom had positive glands on both sides of the abdomen, have had bilateral dissections. Three patients with seminoma were operated upon because the pathological diagnosis was not clearly seminoma. Of the twenty-five patients, eleven had positive nodes. Fourteen patients had negative retroperitoneal glands. Of the eleven patients with positive nodes, eight are living: three have embryonal carcinoma, three have seminoma and two have teratocarcinoma. One patient without positive retroperitoneal nodes (primary teratocarcinoma) is dead from extensive metastases to the lungs and mediastinum, the metastases being composed of choriocarcinoma for the most part. One patient with embryonal carcinoma who showed no positive nodes on the side operated upon is dead due to the development of contralateral retroperitoneal gland metastases, which at the time of their discovery were too extensive for surgery and did not respond to deep roentgen therapy. The other patients with negative retroperitoneal glands demonstrated by unilateral dissection of the retroperitoneal glands on the side of the tumor are all living and free of disease at the present time. Perhaps the most significant contribution of dissection of the retroperitoneal glands is that it provides positive evidence for or against metastasis to the lymph nodes from the testis, which can be used to guide us in further therapy. It should be

pointed out also that in the case of teratocarcinomas or embryonal carcinomas every once in a while the metastatic lesions are less serious than the original tumor, in the sense that either embryonal cell carcinoma or seminoma may make up the metastatic lesions. This can only be determined by examination of the retroperitoneal lymph nodes which sometimes materially changes the prognosis from one which is considered to be very bad to one which is even reasonably good. One could then proceed with radiation of the retroperitoneal area which one might expect would be curative.

Whether retroperitoneal gland dissection of involved lymph nodes may by itself cure testicular cancer in certain cases is not yet certain, because deep roentgen therapy has usually been used as an adjunct following the dissection of retroperitoneal lymph glands.

DISCUSSION

QUESTION: What is indicated in the way of treatment if the patient has both pulmonary metastases and positive retroperitoneal nodes?

DR. LEADBETTER: If one is certain that pulmonary metastases as well as positive retroperitoneal nodes are present, I would not perform resection of the retroperitoneal glands. In such a case one would have to rely on x-ray therapy, and occasionally a response will occur. However, practically every patient with extensive metastatic disease has died. If seminoma were present, x-ray treatment would of course be the therapy of choice.

QUESTION: In the 10 to 12 per cent of tumors associated with hydrocele, how often do you find tumor cells in the hydrocele fluid?

DR. LEADBETTER: I would not expect to find tumor cells in hydrocele fluid, unless the tumor is extensive and actually invades the tunica vaginalis. This is rather unusual. Ordinary hydrocele associated with a tumor of the testis would not contain fluid in which tumor cells could be demonstrated.

QUESTION: May I ask whether Dr. Leadbetter has performed resection of retroperitoneal nodes in two stages?

DR. LEADBETTER: Yes, if a significant number of positive lymph nodes are found on the side of the tumor, questionable or obviously palpable disease involving the lymph nodes on the opposite side, we have performed radical resection of the retroperitoneal gland on the contralateral side as soon as the patient has recovered from the first retroperitoneal operation. Usually an interval of about ten days to two weeks is all that is necessary. So far I have performed three bilateral resections of the retroperitoneal glands.

QUESTION: What is the average age of the twenty-eight patients who have undergone resection of the retroperitoneal glands? What is the morbidity and mortality?

DR. LEADBETTER: Patients range between twenty-five and thirty-five years of age. There has been no significant morbidity and no mortality. Although we used a thoracoabdominal incision we were operating through the chest and not in the chest. We generally close the chest after expansion of the lung without catheter drainage. On three occasions fluid accumulated in the pleural cavity which has necessitated aspiration. The abdominal wounds are not drained and there has been no significant morbidity so far as the abdominal part of the incision is concerned.

QUESTION: Has there ever been any hormonal therapy used in the treatment of testicular tumor?

DR. LEADBETTER: I should have mentioned this. We have had one case which illustrates the possibility of such therapy. The patient was a man of thirty who was found to have a teratocarcinoma of the right testicle. Glands developed in the right inguinal area and the patient was sent to me for further therapy. X-ray examination disclosed no pulmonary metastases. On retroperitoneal exploration, retroperitoneal glands were found, and in addition the liver was found to be studded with metastases which were biopsied and found to be chiefly trophoblastic cancer. I completed a half-hearted resection of the retroperitoneal gland, thought that x-ray therapy would be of no value and finally decided to give testosterone because I had read recently of a woman patient who had choriocarcinoma with pulmonary metastases which disappeared following the use of testosterone. It was my feeling that possibly the testosterone might depress pituitary function and in this way the growth of trophoblastic tissue might be discouraged. The patient was given 100 mg. of testosterone daily for six months. It is now fourteen months after his original operation; the lungs are clear by x-ray and he appears to be perfectly well. He has gained weight and works full time. Physical examination reveals no enlargement of the liver, and although it is too much to expect that this man is cured there has certainly been a remarkable remission. Within the last six months we have dropped his testosterone dosage to 50 mg. a day. Should we stop it or continue it? Is the result purely coincidental or does it have significance? There has been little work done in relation to the possible hormonal or chemical therapy of cancer of the testis. Possibly this should be more thoroughly investigated.

JOHN J. BYRNE (Boston, Mass.): Dr. Chamberlain had a very interesting case recently. How old was the child?

JOHN CHAMBERLAIN (Boston, Mass): One year old.

DR. BYRNE: Teratocarcinoma?

DR. CHAMBERLAIN: Principally mature teratoma. However, microscopic sections refute that, because there has been extension into the tunica and we are a little hard put to know what to do with the patient, whether to excise the scrotum and stop there or do something in addition.

DR. BYRNE: Well, here is your chance to get an expert opinion.

DR. CHAMBERLAIN: I was thinking of that.

DR. BYRNE: What would you do, Dr. Leadbetter?

DR. LEADBETTER: Well, I think this case illustrates the point I was making. The diagnosis of adult teratoma is a dangerous one. Many of these tumors have areas of teratocarcinoma. It is impossible in most cases to section all of the testis, and therefore all diagnoses of adult teratoma should be made with suspicion of underlying teratocarcinoma. I think this child should be treated further. I would probably explore the retroperitoneum on the side of the tumor, if the chest shows no abnormalities, to see if there is any metastatic disease in the nodes. It should be helpful from a prognostic standpoint as well as a guide to further therapy.

QUESTION: Have you taken biopsy specimens of cervical nodes prior to resection of the retroperitoneal gland?

DR. LEADBETTER: We have if there was any indication of enlargement of the cervical nodes. We have not done this routinely.

J. ENGLEBERT DUNPHY (Boston, Mass.): If you did perform a biopsy, you might find the disease unexpectedly.

DR. LEADBETTER: Yes, this is probably so; nevertheless we have performed biopsies only under conditions in which metastatic disease was expected.

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Tumors of the Adrenal Glands

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THE *pheocbromocytoma* is a tumor of the chromaffin tissue of the body; and since chromaffin tissue is rather widely distributed, it follows that the location of these tumors may also vary widely. Naturally, since most of the chromaffin tissue is in the adrenal medulla, this is by far the most common location for these tumors. However, they may occur along the aorta, in the region of the sympathetic ganglions, in the organ of Zuckerkandl at the bifurcation of the aorta, and in such widely diverse locations as the top of the mediastinum and the adductor canal of the thigh.

It is important to point out also that approximately 10 per cent of these tumors are reported to be multiple. Therefore the finding of one does not exclude the possibility that there may be another functioning tumor elsewhere. It is also worth reporting that at least 10 per cent of these tumors are malignant.

The importance of these tumors is that they may produce epinephrine and norepinephrine in large quantities. The clinical symptomatology appears to vary depending on the relative amounts and the action of these two chemicals released into the blood by the tumors. Varying quantities of epinephrine and norepinephrine have been successfully extracted from these tumors many times. The diagnosis is to be considered when symptoms which may be caused by the action of epinephrine and norepinephrine are encountered.

The symptoms most common are those associated with vascular and blood pressure phenomena. Classically, the description is that of hypertension in episodes—in "attacks," the patient usually will say. Associated with these attacks are headache, palpitation, sometimes extreme sweating, nausea and vomiting, and sometimes syncope and exhaustion. This is the classic picture, and it is the picture with which the tumor was first associated. However, it has become apparent over the last ten or fifteen years that the tumor can also produce sustained unremitting hypertension. Therefore, some people have gone so far as to suggest that some of the diagnostic tests I shall describe should be used in every instance of serious essential hypertension.

Sweating is the next most commonly reported symptom according to the literature. Vasomotor phenomena are common. These consist of blanching alternating with rubor of the skin of the face or sometimes of the extremities. They probably have to do with variations in the amount of epinephrine and norepinephrine produced. An elevated temperature has been reported rather consistently. There is often associated diabetes, or at least glycosuria. As is commonly known, one of the effects of epinephrine is the production of an elevation in blood sugar. The fasting blood sugar is quite commonly above 120 mg. per cent.

Another common and often deceiving symptom is a general elevation of oxygen requirement and, therefore, elevation of the "basal" metabolic rate which may be mistaken for Graves' disease. In certain instances thyroidectomy has been carried out, unsuccessfully of course. In other instances unsuccessful antithyroid therapy has been instituted. Just as a diagnostic point, it is worth mentioning that the protein-bound iodine is not elevated in patients with pheochromocytoma and that fact should be an important diagnostic distinction.

Finally, one of the important symptoms is autonomic imbalance involving smooth muscle functions. These patients may become very ill with ileus and serious abdominal distention. Apparently they are also more prone to sudden death, particularly following operations or other situations of stress.

These, then, are the symptoms which must be kept in mind if one wishes to pick up these tumors. There are certain provocative tests which may be used in instances in which this

situation is suspected. One of the earliest described was the relationship of posture to precipitation of hypertensive episodes when an adrenal tumor exists. The patient bends his body in such a way as to squeeze the adrenal tumor and an attack ensues. Attacks may also be precipitated by massage over a palpable tumor.

Epinephrine or histamine given in amazingly small doses may precipitate a crisis. This is a dangerous way of approaching the problem; and with our other drugs and tests, it is not necessary. The episode produced by the injection of 0.025 mg. of histamine base may actually be serious enough to threaten life. Methylcholine and tetraethylammonium bromide or chloride may also be used as precipitating agents, and these seem to be less dangerous. The thing one looks for here is an elevation of blood pressure in a patient who normally has normal blood pressure.

In patients with sustained hypertension in whom you suspect pheochromocytoma there are several diagnostic tests which can be used. In these, the effect is to drop the blood pressure presumably by specific but as yet unexplained actions which have to do with the presence of an unusual amount of epinephrine and norepinephrine in the circulating blood. Among these drugs are benzodioxane (33F) and regitine.®

Most recently a suggestive diagnostic test has been reported in extending the use of benzodioxane which may cause not only a fall in blood pressure but also apparently a fairly reliable reduction in urinary flow only in the presence of pheochromocytoma. That has to be borne out by further experience. I should say that in all these instances, both in the provocative tests and in the diagnostic blocking tests, there are examples of false negatives and false positives, so that you cannot rely on any one of them, unfortunately.

Finally, it seems that urinary assay for norepinephrine and epinephrine or precursors may become a reliable diagnostic test. Some successes have been reported in finding abnormally elevated amounts of these materials in the urine in cases of pheochromocytoma. If this method is reliable, it will probably be better than anything else we have. It may even be possible some day to test the blood for these circulating agents.

Once the diagnosis is made one has to think of localization. If there is a palpable tumor, it is easy. If there is an obvious tumor by x-ray, either pyelogram or plain abdominal film, that is easy. Some would suggest the introduction of air or oxygen—we use oxygen now—for outlining the retroperitoneal space. Personally, I have little enthusiasm for this technic because it has its own risks.

In the end one may have to resort to exploring the patient in order to settle the problem. In exploring for pheochromocytoma, one must be prepared to look at all the possible areas which may be involved. The trick which everyone is anxious to accomplish is to manipulate the tumor very little until he is able to control its venous return because manipulation of the tumor often precipitates very striking rises in blood pressure on the operating table. This can be regulated by preparing the patient with an intravenous infusion, and having available benzodioxane or regitine for use as a constant intravenous drip during this phase of the procedure. It usually works very well.

After the removal of the last bit of functioning medullary tumor, hypotension should develop rather rapidly while the patient is on the operating table. If hypotension does not develop, the surgeon must look for another tumor.

Now the situation is reversed. Intravenous infusion of benzodioxane or regitine is stopped and epinephrine and norepinephrine is started, usually intravenously. Often this must be continued for as long as a day or two depending on the patient's blood pressure and further developments after the operation.

Several people have also suggested that because one often has to remove adrenal cortical tissue, it may be wise to give these people supporting cortisone for hypoadrenocorticism. This move has seldom seemed necessary. Patients are often much benefited by removal of a pheochromocytoma and, on the other hand, failure to remove a functioning tumor is disastrous. Therefore I recommend a more aggressive willingness to explore for these tumors in questionable situations.

Adrenal Cortical Tumors. Now, let us go on to hyperfunctioning of the adrenal cortex. I think one should start historically. I want to specify that I am going to stick to hyperfunctioning of the cortex which produces the ailment we call Cushing's syndrome. There are other hyperfunctioning tumors of the cortex which produce estrogens, but they are

quite rare and are usually malignant; therefore we will leave them without further discussion.

In 1912 Cushing first described the syndrome which bears his name. His patient presented a classic picture in many ways as we now look back on it. She was a young woman who was obese, with the characteristic distribution of fat around the head, neck and trunk, with thin extremities, hirsutism, amenorrhea and diabetes. Cushing suggested at that time that she might have a disease which was fundamental to the pituitary gland. However, in the original write-up—and this is interesting—he suggested that the adrenal glands might also play an important role. He had found at least one similar instance in the literature in which an adrenal tumor had been found at autopsy.

There was a long hiatus of time without much further notice of the disease, and it was not until 1930 that Cushing saw another patient with a similar syndrome. The second patient was a man who was given x-ray therapy to the pituitary, as were several of Cushing's subsequent patients. This first man had a very striking clinical remission, and Cushing decided that this disturbance was one in which the anterior pituitary adenoma finally found at autopsy played a dominant etiological role.

Subsequent experience has made us modify this point of view, at least in part. There is little doubt in our minds, I believe, that there is a relationship between the anterior pituitary and the adrenal in this disease; yet the mere fact that I can talk about functioning adrenal tumors which produce this disease shows that the anterior pituitary causation suspected by Cushing may not be the only one.

It was not until 1935 that another possible cause was really first discovered. A patient with classic Cushing's disease was given pituitary radiation and failed to respond. After a long and rather unfortunate course she died with multiple metastases from adrenal cortical carcinoma.

Later it was shown by Crooke that adrenal tumors with this type of syndrome may be associated with a change in the pituitary basophils which has been called "smudging." There is still doubt as to whether the changes observed in the pituitary basophils are the result of an unusual amount of circulating adrenal hormone or are primary changes which may be the factor which brings about the formation of the adrenal cortical tumor.

Cushing's syndrome is a rare disease also. There are about 300 cases recorded in the literature. Three pathological types are encountered: I cannot possibly avoid talking about hyperplasia as well as tumors here. It will give you some idea of the relative occurrence of the pathological types to know that in a series of forty-six patients with Cushing's disease about two-thirds (twenty-seven) proved to have hyperplasia of the adrenal cortex [*1*]. There were seventeen tumors, twelve benign and five malignant. Two patients were unclassified pathologically because there was never any operation.

I shall discuss carcinoma of the adrenal cortex briefly only to say that it is a very unsatisfactory disease to treat. To the best of my knowledge, no patient has ever been cured. The tumor grows quietly with few early symptoms, and by the time one recognizes the presence of the disease there are often extensive metastases.

On the other hand, benign adenomas may exist for long periods and the clinical course is determined by the intensity of the metabolic changes. This is also true of hyperplasia. Our usual problem is to distinguish between hyperplasia and benign tumors.

When does one suspect Cushing's syndrome? Some thirty-three or thirty-four factors have been described in the literature as characteristic of Cushing's disease, and no one patient that I have ever seen or read about has all these, so that the disease pattern is variable. Naturally, if you accept the fact that there are many, many different adrenal cortical hormones being produced, you would expect to see variability in the pattern in accordance with the relative amounts of the various hormones secreted by the abnormal adrenal.

There are, however, several constant symptoms which one can cull from the literature and experience:

Almost all these people, men and women alike, will either complain of muscle weakness on physical exertion or tell you after cure of their disease that now they notice that their physical strength is much better. We believe this symptom relates in some fashion to protein metabolism. These patients just are not making muscle well to replace that which breaks down with normal use.

Osteoporosis is probably almost as common. Dr. Albright used to say that you should not

make the diagnosis of Cushing's syndrome without osteoporosis; but there are one or two cases recorded in which there was no osteoporosis.

The change in physical appearance which is so obvious is easy when it is characteristic i.e., the moon-face and the buffalo hump.

Abdominal striae are quite characteristic. These are not the striae of pregnancy. They are active and violaceous, and with the cure of the disease they become white and inactive. We look upon them—and I think this is Dr. Cope's term—as "fractures of the derma of the skin." Under the normal stresses of activity the derma fractures and separates, and one can see through the epithelium the underlying blood vessels.

Hypokalemic alkalosis is quite common. The glucose tolerance curve is of the "diabetic" shape, although frank diabetes is not common. Elevated 17-ketosteroids are quite common but not necessarily always present. Very commonly, if you have the laboratory facilities to test them, you will find elevation of the 11-oxysteroids in the urine. This test seems quite reliable if the 11-oxysteroids are elevated.

Finally, one must not forget that many of these people have serious mental symptoms. I am fond of pointing out that Dr. Hannibal Hamlin a few years ago picked one of these people out of the insulin shock therapy ward of a state mental institution. She was being treated for supposed schizophrenia. After the removal of her adrenal cortical adenoma she is now a normal person.

When one suspects the diagnosis, one must decide where the tumor is. What I said about adrenal medullary tumors applies here, also. I will say just briefly that I do not especially like to use any kind of air injection. If there is no obvious tumor in either adrenal by plain abdominal film, I suggest that one explore the right side first. The reason for this is that the soft tissue of the adrenal is often in contact with the posterior surface of the liver and may actually be of the same consistency so that x-ray will not reveal it. Exploration may be required before the tumor is discovered. On the left side one can usually see the tumor in a good plain abdominal film.

The surgeon is the man who makes the pathological diagnosis, usually at the time of operation. The pathologists have had difficulty in deciding just what the changes in the adrenal were. There is reason to think some progress is now being made with special staining technics.

For this type of operation you do not have to have a large incision. I like to take out either the eleventh or twelfth rib and go through the pleura, diaphragm and Gerota's fascia, which brings you right down on the adrenal. There are other ways of doing this, but each operator develops his own preference.

The surgeon's first view is almost always diagnostic. If he sees the tumor, it is very simple and he knows what he has to do. These tumors are seldom multiple. If he finds no tumor on the side on which he operates, he will find one of two other things: (1) He may find an atrophic adrenal, that is to say, thinned out, pale and smooth. This implies a tumor on the opposite side. (2) If he does not find an atrophic adrenal, he finds hyperplasia of the cortex. The appearance of hyperplasia is the converse of atrophy, namely, increase in convolution and thickness. If he finds hyperplasia, he knows that he probably has a diffuse process on both sides.

There is a stage between hyperplasia and tumor which is very interesting from the theoretical point of view. We have seen three people in whom we have called the pathological type "nodular hyperplasia." This is merely a descriptive term. In this condition there is diffuse thickening of the cortex but there are also several nodules. The whole gland seems to be involved. In some of these glands there are as many as five or six nodules. It seems theoretically possible that the following sequence of events may occur: Some factor starts the adrenal cortical hyperplasia; it may be that some abnormality of the pituitary causes generalized hyperplasia of the adrenal cortex in most instances. Occasionally, one or several areas may become increasingly hyperplastic and form nodules. If the concentration of activity in that area is sufficient over a long period of time, perhaps the nodule may progress to be a true tumor and the rest of the cortex of the gland becomes atrophic. This is rank speculation since there is little evidence for it.

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DISCUSSION

JOHN J. BYRNE (Boston, Mass.): Does anyone have any comment or question on this interesting subject?

QUESTION: In what places did you find most of the ectopic tumors of the adrenal?

DR. RAKER: I think the literature says that something like 80 per cent are in the abdominal cavity. And if they are not in the adrenal (talking about pheochromocytomas mostly), they may be around the celiac axis, along the aorta or in the organ of Zuckerkandl. Those would be the next places to look. They have been found in the testis. They have been found along the iliacs. They have even been found up in the mediastinum.

QUESTION: If you have a large malignant tumor on one side, would you recommend exploration on the opposite side as routine or would you wait for physiological measurements?

DR. RAKER: I think I would wait for physiological measurements. Are you speaking of pheochromocytoma or cortical tumor?

ANSWER: Cortical tumor.

DR. RAKER: Actually, of the six malignant cortical tumors of Cushing's syndrome I have seen, only one has ever been operable. Most of them had some distant metastasis, i.e., to lung, bone, liver or lymph nodes. One or two had local inoperability because of growth into the liver or a major blood vessel. One man underwent a rather extensive resection with recurrence within three or four months with a pulmonary metastasis, and died.

QUESTION: Do you find that the malignant cortical tumors are as physiologically active as the benign?

DR. RAKER: Yes, and sometimes they have rather bizarre pictures. They may change from time to time. The man I mentioned had a great deal of subcutaneous hemorrhage which has been one of the symptoms reported. This was the cause of his death, and it was the cause of another death of which I know. These people are also susceptible to infection, apparently, and that fits in with our knowledge of cortisone and its effect. One of the main causes of death has been some uncontrolled infection which is superimposed upon this disease.

QUESTION: How do you handle the urinary assays in these cases? There have been cases when the clinical picture was outstanding but the laboratory failed to confirm the diagnosis, yet a tumor or hyperplasia was found.

DR. RAKER: That is hard to answer. The assay of 17-ketosteroids is not terribly reliable. If you are interested, you will find that Drs. Forbes and Albright have analyzed this problem in the literature. Briefly, many patients may have normal instead of elevated 17-ketosteroids. If there is an unusually high 17-ketosteroid, it indicates either hyperplasia or a tumor. If there is a normal or low 17-ketosteroid, it indicates either hyperplasia or a benign tumor. Approximately 75 to 80 per cent will have some elevation of the 17-ketosteroids. Much more accurate is the 11-oxysteroid assay. I know of only one instance in which that was not elevated in which Cushing's syndrome was proved, and in this instance there was elevation of the 17-ketosteroids.

DR. BYRNE: Dr. Whitelaw, since you have had experience with adrenal tumors and pheochromocytomas, would you have any comment to make?

DR. WHITELAW: In our experience the majority of these have been on the left and we explore that side first.

DR. RAKER: That is true, but I think the proportion in all the literature is not strikingly different. In some 300 pheochromocytomas reported I think the incidence is just a little bit more on the left.

DR. BYRNE: What incision are you using now, Dr. Whitelaw?

DR. WHITELAW: We take out the twelfth rib and divide the diaphragm on both sides.

DR. BYRNE: What incision would you use in pregnancy?

DR. RAKER: When a surgeon has a special interest in a disease, he is most likely to select the method of handling it that he likes best and then justify it. If the patient is very thin—not seen very often in Cushing's disease—you can operate very satisfactorily through an abdominal incision. The big advantage is that you can look at both adrenals at the same time. If the patient is a big, fat person or pregnant, I would certainly favor using some lateral approach. It is just easier for me.

QUESTION: Do you believe that there is any place for the ACTH test, so called?

DR. RAKER: Yes. I did not go into that, but I think the test is probably good.

QUESTION: In Cushing's disease caused by adrenal cortical hyperplasia rather than adenoma, is the hyperplasia more often bilateral than unilateral?

DR. RAKER: Yes, almost always bilateral.

QUESTION: How much tissue do you remove in hyperplasia?

DR. RAKER: May I give an analogy? Surgical management of the patient with Cushing's syndrome caused by adrenal cortical hyperplasia is similar to the problem of the surgical treatment of hyperthyroidism. If you take out enough of the overfunctioning endocrine gland to cure the patient, you run the risk of myxedema in the thyroid or Addison's disease in the adrenal. If you want to be sure to cure the patient, you will remove all of both adrenals and accept the fact that you are going to have to support this patient with cortisone indefinitely. Personally, I would like to leave a little bit of adrenal cortex because you hope that perhaps you can carry these people to the point

where they do not require any supportive therapy. This raises the additional question of whether the disease will return if you leave any hyperplastic cortex. We do not know.

I have not gone into the problem of postoperative management. We have usually given these people cortisone preoperatively and during the operation, and then tapered it off during a period of two or three weeks postoperatively down to a maintenance dose of 25 mg. per day or less if they require it. If you do not do this and you remove a functioning adenoma, of course you run the grave risk of precipitating acute addisonian crisis because the remaining atrophic adrenal cannot support the patient until some time has gone by. This is worth pointing out.

Ulcerogenic Tumors of the Pancreas

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THE pancreas has long been under suspicion as having a possible relationship to the etiology of gastroduodenal ulceration [*1,10*]. The report in 1955 of two cases of primary benign jejunal ulceration [*13*] associated with non-beta islet cell tumors of the pancreas tended to confirm such an association.

Several clinical examples will be presented to illustrate the clinical course of the patient with an ulcerogenic tumor of the pancreas. The selected cases will illustrate some of the serious problems common to these patients, as well as the variety of surgical approaches that were utilized. Lastly, a clinical example will be included to suggest the possibility that hyperplasia of the islets may possibly be implicated in the severe ulcer diathesis requiring total gastric resection to control the acid factor.

A study of these cases suggested the following diagnostic triad: (1) A fulminating ulcer diathesis exists, especially when the upper jejunum is primarily involved or secondary gastrojejunal ulceration follows radical surgical intervention. Despite adequate therapy consisting of intense medical as well as radical surgical, and on occasion additional radiation therapy, the tendency to recurrent ulceration persists. (2) Next in the triad is a marked gastric hypersecretion as determined by a twelve-hour nocturnal gastric aspiration. The twelve-hour aspiration studies may show as much as 2 or 3 L. of gastric juice with a total amount of free hydrochloric acid which may exceed 300 mEq. in contrast to the normal twelve-hour value of 18 mEq. The capacity to produce huge volumes of gastric juice tends to persist as long as any gastric-secreting mucosa is retained. (3) The triad is complete if a non-beta islet cell tumor of the pancreas is verified. These findings are in contrast to the triad of Whipple in which there is associated a beta cell adenoma and symptomatology due to the overproduction of insulin.

Although the possibility of a tumor of the pancreas producing marked gastric hypersecretion with ulcer formation appears to rest on a firm clinical basis, there is unfortunately as yet no convincing evidence as to the mechanism or the predominate islet cell involved. In the original report it was suggested that perhaps the alpha cell was in predominance and that glucagon, the antagonist to insulin, could be in overproduction and account for the marked gastric hypersecretion. As shown in Figure 1, any or all of the types of islet cells (i.e., alpha, gamma, delta, but excluding the beta cell), must be considered until further clinical, experimental and pathologic studies have isolated the offender beyond any reasonable doubt. It is possible to theorize that one or more of the islet cells in ordinary numbers may play a role in the normal production of gastric juice. When present in excessive numbers as in an adenoma, or when associated with hyperplasia of the islets, hypersecretion and a severe ulcer diathesis develop.

In addition to the four cases operated upon on the surgical service of the Ohio State University, twenty additional cases were collected by Ellison [*2*]. Since his published review in 1956, he has been able to gather data on another twenty-four cases, giving a total of forty-eight cases [*3*]. Eight of the more recent cases have been diagnosed preoperatively on the basis of the triad initially suggested.

The clinical course of four cases demonstrating the problems associated with this triad will be presented. In three patients an islet cell tumor was found, while in one patient hyperplasia of the islet cells was suggested.

CASE REPORTS

CASE 1. C. H., a fifty-seven year old white woman, was first seen in 1947 when she presented a history of epigastric distress of about ten years'

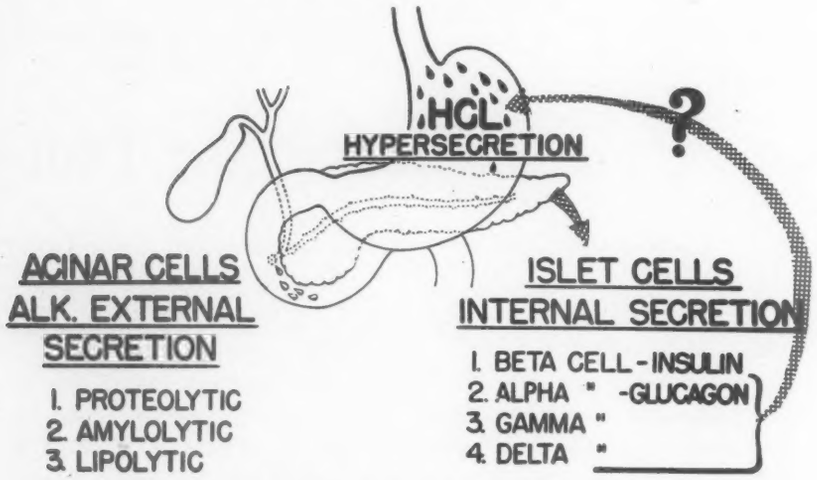

FIG. 1. Known and postulated physiologic functions of the pancreas.

duration. Two years previously she had undergone gastroenterostomy with relief of her symptoms for about six months, following which her symptoms recurred and gradually increased. Since the gastroenterostomy, she had had a 30 pound weight loss from her usual weight of 150 pounds. The patient, incidentally, had had diabetes mellitus for the seven years prior to her admission and required about 25 units of protamine zinc insulin daily.

Gastric analysis on admission showed 2,150 cc. for a twelve-hour secretion with 129 mEq. of free hydrochloric acid. An active duodenal ulcer was demonstrated by radiographic studies. At surgery in October, 1947, peptic ulceration of the duodenum was confirmed and bilateral vagotomy was performed. During the procedure a hard tumor nodule was visualized in the pancreas and was biopsied. The frozen section studies were inconclusive in differentiating chronic pancreatitis from malignancy, so the mass was not resected.

The twelve-hour gastric secretion dropped to 570 cc. in volume, but it was disappointing to find 56 mEq. of free hydrochloric acid. This strongly suggested an incomplete vagotomy. Permanent microscopic sections of the pancreatic biopsy showed what was interpreted as an acinar cell carcinoma. Three weeks later the patient underwent resection of the body and tail of the pancreas, together with splenectomy.

Following the partial pancreatectomy with removal of the tumor, the twelve-hour gastric secretion fell to below 100 cc. and showed no free hydrochloric acid. This clearly implicated the tumor of the pancreas as the origin of the stimulus for the high acid values which persisted after vagotomy. Two years later, in 1949, the patient was readmitted with a complaint of epigastric and back pain, but with a weight of 145 pounds. Gastric analysis showed no free hydrochloric acid with histamine stimulation, and upper gastrointestinal x-rays showed no evidence of an ulcer. The patient was discharged as having probable recurrence of pancreatic carcinoma. She was readmitted in coma for the final time two years later, almost exactly four years following the partial pancreatectomy. At autopsy she was found to have an acute subdural hematoma. In addition, the liver was practically replaced with metastatic tumor, and the pancreas contained dense sheets of tumor. There was no evidence of gastroduodenal ulceration. On review of the miscroscopic sections it was determined that this was a case of a non-beta islet cell carcinoma instead of an acinar cell carcinoma, which had previously been reported.

Comments: This case demonstrates the value of inspecting the pancreas at the time of surgery for gastroduodenal ulceration. If this tumor had not been found, the vagotomy would have been condemned as either incomplete or ineffectual in controlling the acid factor. The absence of subsequent ulceration despite extensive recurrence of the malignant islet cell tumor might be explained on the basis of a change to a less differentiated tumor.

CASE II. J. M., a nineteen year old white woman, was first seen in January, 1954, with a complaint of epigastric pain. Two years previously, at the age of seventeen, the patient underwent a negative abdominal exploration with an incidental appendectomy because of abdominal pain. One year later she had two jejunal ulcers, located about 6 inches from the ligament of Treitz, which perforated simultaneously. A few months following the surgical closure of these ulcers, she had two episodes of intestinal obstruction, one of which required laparotomy for release of adhesions [7]. In the six months prior to admission the patient had lost 59 pounds from her original weight of 180 pounds.

On admission a 12-hour gastric aspiration obtained 2,800 cc. of secretion with 308 mEq. of free hydrochloric acid. A repeat test the following day obtained 2,400 cc. of secretion containing 259 mEq. of free hydrochloric acid. An upper gastrointestinal x-ray series showed a possible jejunal ulceration.

At surgery subdiaphragmatic vagotomy and radical gastrectomy with fundusectomy and gastroduodenostomy were performed, leaving a residual pouch 6 by 8 cm. in size. The patient had a relatively short period of relief followed by return of severe mid-epigastric pain with radiation to the back and accompanied by occasional vomiting.

A series of gastric secretion studies showed that despite the small remnant of stomach and vagotomy, the patient was again able to produce as much as 2,000 cc. of gastric secretion over a twelve-hour period with amounts of free hydrochloric acid which gradually increased from 32 to 84 mEq. by August, 1954. She had had such a radical resection that it was decided to give 2,000 r of x-ray therapy to the gastric remnant in an effort to control her production of acid without subjecting her to total gastrectomy. She had hardly completed 1,900 r of therapy when excruciating burning pain developed in the epigastrium which was unresponsive to medication and required constant gastric aspiration. She had one short period of hospitalization at this time, and gastric aspirations were diminished to 1,250 cc. with only 21.5 mEq. of acid. However, about two weeks after the x-ray therapy was discontinued the gastric secretion was 1,350 cc. with 82 mEq. of free hydrochloric acid. In October, 1954, the patient was again admitted with the complaint of almost continuous epigastric pain. She was fasted for forty-eight hours to test for a possible functioning beta islet cell tumor with hyperinsulinism. Repeated blood sugar determinations failed to demonstrate evidence of hypoglycemia. However, during the patient's forty-eight–hour fast, her symptoms markedly increased and she required narcotics for pain. Fearing perforation, an emergency gastrointestinal study was done which showed a gastroesophageal ulcer and a penetrating stomal ulcer at the gastroduodenal junction.

Total gastrectomy was then considered necessary, and at the time of surgery a sealed-off perforation of an esophageal ulcer was found. In addition a 1½ inch ulceration had practically replaced the posterior side of the gastroduodenal anastomosis. The duodenal stump was closed and a Roux-en-Y type of esophagojejunostomy was performed. The adrenal glands were explored for tumor and none found. However, upon exploring the pancreas, several small nodules were found on the anterior aspect at the tip of the pancreas which appeared to be lymph nodes. However, on microscopic examination one of these nodules showed a non-beta islet cell carcinoma of the pancreas, and a second nodule which was also removed proved to be a lymph node containing islet cell tumor. The patient's convalescence was complicated by an esophageal jejunal stenosis which was perforated during attempts at dilatation.

The patient was asymptomatic when readmitted two and a half years later in March, 1957. She had retained her ideal weight of 122 pounds.

Comments: This patient demonstrates the most classic finding in favor of the diagnosis of ulcerogenic tumor of the pancreas, a primary perforation of an ulcer in the upper jejunum. Her clinical course indicates the justification for total gastrectomy in the presence of these tumors, regardless of the patient's age.

Case III. C. K., a forty-four year old white woman, was first seen in May, 1956, with a complaint of persistent upper abdominal pain associated with nausea, vomiting and tarry stools. She was referred with a diagnosis of ulcerogenic tumor of the pancreas [6]. Three years previously an operative procedure for lysis of adhesions had been performed. Two and a half years previously a perforated jejunal ulcer required closure, and again nine months before admission another perforated jejunal ulcer was closed. In the nine months before admission the patient lost 15 pounds and was given a total of 22 pints of blood because of melena.

On admission the patient was seen to be an emaciated white female appearing chronically ill and weighing 85 pounds. A twelve-hour gastric aspiration produced 2,700 cc. of secretion with 27 mEq. of free hydrochloric acid. A glucose tolerance test showed a diabetic curve. An ulcer crater in the proximal jejunum was demonstrated by barium meal examination.

At surgery three grossly identifiable pancreatic tumors were found on the surface of the body of the pancreas, confirming the admission diagnosis. The body and tail of the pancreas were removed, and subtotal gastrectomy (removing two-thirds of the stomach), vagotomy and Billroth 1 anastomosis were performed. The stomach showed severe hypertrophic gastritis. In addition to the adenomas the microscopic sections of the pancreas showed diffuse islet cell adenomas of the non-beta cell type. The convalescent course of the patient was satisfactory, but a twelve-hour gastric analysis just before her discharge two weeks postoperatively showed 950 cc. of secretion with 90 mEq. of free hydrochloric acid.

After a two-week asymptomatic period at home, the patient had a recurrence of epigastric discomfort associated with lumbar pain and nausea. She had a 10 pound weight loss in one week and was readmitted in July, 1956, weighing 77 pounds. An upper gastrointestinal x-ray series showed a large duodenocolic fistula which was confirmed by

barium enema. At operation on the fourth hospital day, total pancreatectomy, duodenectomy and end-to-end gastrojejunostomy as well as closure of the duodenocolic fistula were performed. The ampulla of Vater was reimplanted into the jejunum, which had been mobilized to effect a Billroth II type gastrojejunal anastomosis. Gastrostomy was used for decompression.

Diffuse involvement of the islets again was found on microscopic examination. In addition, an islet cell adenoma could be seen in the wall of the duodenum. One week postoperatively the twelve-hour gastric secretion was 800 cc. with 16 mEq. of free hydrochloric acid. The gastrostomy tube was removed on the fourteenth postoperative day, but it became evident that this tube had created a permanent gastrocutaneous fistula. The patient's diabetes was very labile and has remained so to the present with 4 or 5 units of regular insulin often resulting in insulin shock, and 2 to 3 units allowing hyperglycemia to occur. The patient was given pancreatic supplements (viokase, 9 to 12 gm. daily) following total pancreatectomy. During the two months postoperatively the gastrocutaneous fistula persisted despite one surgical attempt at closure. She was then given 3,700 r units of x-ray therapy to the remaining gastric pouch in the hope of decreasing the production of free hydrochloric acid and permitting the gastric fistula to heal. However, the acid digestion of the abdominal wall continued.

In October, 1956, total gastrectomy with esophagojejunostomy was performed with great technical difficulty. The patient's subsequent course at times has been precarious and has required almost continuous hospitalization in her own community, partly to regulate her insulin requirements. Recent reports [6] indicate that her weight fluctuates between 76 and 80 pounds and that she does occasionally have difficulty in swallowing.

Comments: A past history of repeated perforated jejunal ulcerations suggested the diagnosis of an ulcerogenic tumor of the pancreas. Removal of the cephalic and gastric phase of secretion combined with hemipancreatectomy removing three grossly visible adenomas did not control the ulcer diathesis. Removal of the duodenum and the remainder of the pancreas demonstrated a diffuse form of adenomatous involvement of the islets which was present even in the wall of the duodenum. The possible presence of hidden metastases may explain the persistent ulcer diathesis until total gastrectomy was performed.

Her clinical course supports the wisdom of performing total gastrectomy at the time an original adenoma is resected since diffuse islet cell involvement is an ever present danger.

CASE IV. A. F., a fifty year old white man, was first seen in 1954 with epigastric distress. Twelve years previously a standard gastric resection with a Billroth II type of anastomosis for intractable duodenal ulcer had been performed. One year later closure of a perforated marginal ulcer was required. Within a few months subdiaphragmatic vagotomy and resection of about half of the remaining gastric remnant were accomplished. Within two years another marginal ulcer had developed and transthoracic supradiaphragmatic vagotomy was performed. He continued to be miserable with symptoms suggestive of recurrent marginal ulceration. When first seen in 1954, the presence of a marginal ulcer was again proved, and it was decided that nothing short of total gastrectomy would insure this man a reasonable amount of comfort.

Accordingly, total gastrectomy was performed, and at the time of surgery a recurrent marginal ulcer was found. Although the body and tail of the pancreas were searched carefully, no gross islet cell tumor was found. Since his clinical course strongly suggested the triad of an ulcerogenic tumor of the pancreas, the distal half of the body and tail of the pancreas was resected.

Miscroscopic study with the use of special stains [5] indicated that not only might there be an increased number of islets but also a greater proportion of non-beta to beta cells.

At the time of total gastrectomy his weight had fallen to 105 pounds (from his usual weight of 150 pounds). Two years following total gastrectomy, his weight was up to 123 pounds and he was asymptomatic. However, since this time the patient has been lost to follow-up and no information can be obtained.

Comments: Islet cell adenomas do not always account for the fulminating ulcer diathesis which may in rare instances require total gastrectomy. Hyperplasia of the islets is suggested as a possible explanation, as illustrated in this patient.

Perhaps biopsy of the body and tail of the pancreas is more frequently justified in the evaluation of the patient with recurrent ulceration despite previous radical surgical measures.

PATHOLOGY

This pancreatic tumor associated with gastric hypersecretion has the typical characteristics of an islet cell adenoma. Like the beta cell adenoma, its presence can be determined by gross examination in many instances. When it occurs as a single recognizable mass, the location is in the body or tail of the pancreas two-thirds of the time. In some cases the majority of the islets are involved and the adenomas are detected only microscopically. Regardless of size, two-thirds of the tumors show the characteristics of malignancy and may metastasize to the liver. Whether or not

the metastases are functional may depend upon their degree of differentiation.

The identity of the cell type of the ulcerogenic tumor has not been easy even with specific staining technics, and indeed there still remains some question among pathologists as to which of the islet cells, excluding the beta cells, are involved.

It appears in some instances that even though no actual adenoma exists, hyperplasia of the islet tissue may account for a fulminating ulcer diathesis. This could be likened to the parathyroid gland where hyperplasia of the cells results in a clinical and laboratory picture indistinguishable from that produced by a true adenoma. One may be misled by an apparent increase in the number of islets of the pancreas, however, since the normal pancreas has a wide variation in the number of islets present. Perhaps the most helpful criterion will prove to be an increase in the proportion of non-beta to beta cells.

COMMENTS

While the mechanism responsible for the ulcer diathesis remains unsolved, it is apparent that a powerful stimulus for the stomach to produce hydrochloric acid does exist. The volume of gastric juice rich in hydrochloric acid is so large that any medical attempts at control short of constant gastric suction are doomed to failure. The clinical course of these patients clearly shows that the overproduction of hydrochloric acid is not appreciably altered by removal of both the cephalic as well as the gastric phase of secretion. Likewise, radiation of the fundic glands (2,000 r), which effectively reduces the acid values in the majority of patients [*8*], has only a weak transient effect in the patient with an ulcerogenic tumor of the pancreas. Failures have been observed when the patient by actual measurement had only a gastric pouch 6 cm. by 8 cm. remaining.

Although the complications of duodenal ulcer are uncommon in the presence of pregnancy [*12*], Patton [*9*] has observed a fulminating ulcer diathesis which ended in a fatality within three weeks following delivery. An islet cell tumor of the pancreas with metastases to the liver was verified.

The tumor when found, should be quick frozen under sterile conditions in the hope that biologic assays can be carried out. Such studies should eventually either further clear or definitely implicate the pancreas as a villian long suspected, but never directly implicated.

The presence of a primary non-specific and benign ulceration of the upper jejunum would appear to be almost pathognomonic of an ulcerogenic tumor of the pancreas. The previously reported jejunal ulcers have been invariably associated with a high degree of recurrence and a high mortality [*4,11*]. Because of insufficient attention to the pancreas in these patients, however, conclusions regarding the presence or absence of an ulcerogenic tumor cannot be made.

The finding of huge volumes of gastric juice by a twelve-hour constant nocturnal aspiration should also raise the suspicion of an ulcerogenic tumor. In the absence of pyloric obstruction, the recovery of 2 to 3 L. of gastric juice with a high mEq. value in free hydrochloric acid should focus attention to the pancreas.

Lucky is the surgical service that does not have one or more patients with duodenal ulcer who continue to have recurrent ulceration, regardless of the type of operation or the extent of the resection. Evidence has been presented which would indicate that the presence of an ulcerogenic adenoma of the pancreas would condemn any operative procedure short of total gastrectomy to failure. The possiblity of a tumor or hyperplasia of the islet cells of the pancreas should be considered and the appropriate procedure followed to prove the diagnosis as well as to control the ulcer diathesis.

The principles of surgical treatment must be considered elastic until sufficient clinical experience has accumulated. Originally it was hoped that a conservative gastric resection could be carried out when a visible tumor of the pancreas was verified and excised. However, the frequency of multiple tumors combined with the possibility of metastases has tended to produce recurrent difficulty in the majority of cases. For this reason the vicious circle in the overproduction of acid gastric juice can most certainly be broken by removing all of the acid-producing area by total gastrectomy. Although this is a very radical procedure, regardless of the age of the patient, it would appear to be more effective as well as better for the patient than total pancreatectomy. Total gastrectomy, therefore, should accompany the surgical verification of an ulcerogenic tumor of the pancreas. (Fig. 2.)

On occasion the patient continues to have a

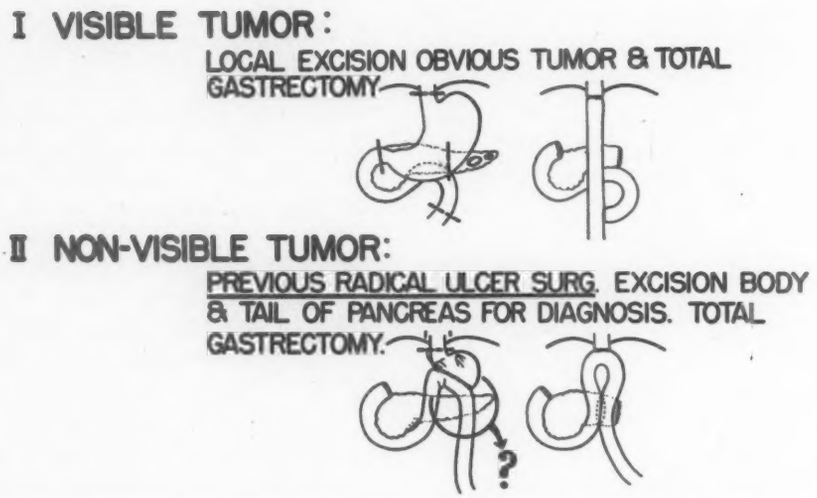
I VISIBLE TUMOR:
LOCAL EXCISION OBVIOUS TUMOR & TOTAL GASTRECTOMY
II NON-VISIBLE TUMOR:
PREVIOUS RADICAL ULCER SURG. EXCISION BODY & TAIL OF PANCREAS FOR DIAGNOSIS. TOTAL GASTRECTOMY.
?

FIG. 2. Suggested principles of surgical treatment for ulcerogenic tumor of pancreas.

marked ulcer diathesis despite previous very radical surgical procedures. The pancreas should be thoroughly examined for tumor at the time of operation. Even though none are found left hemipancreatectomy is justifiable to establish the presence of either small and diffuse involvement of the islets by tumor or hyperplasia. Total gastrectomy is again the procedure of choice, although prolonged postoperative rehabilitation is always mandatory when the entire stomach is removed. It is earnestly hoped that clinical and experimental studies will continue to determine if the triad of the ulcerogenic tumor is valid. Regardless, investigation into the possible role of the pancreas in the production of hydrochloric acid may throw some light on the baffling and all too common clinical syndrome of gastroduodenal ulceration.

CONCLUSIONS

1. The triad consisting of fulminating ulcer diathesis and marked gastric hypersecretion associated with a non-beta islet cell tumor of the pancreas is reiterated.

2. Three clinical examples of proved non-beta islet cell adenoma are presented to show (1) the fulminating ulcer diathesis with failure of standard methods of medical, surgical and radiation therapy; (2) the variations in the gross pathology of the ulcerogenic tumor; and (3) the justification for total gastrectomy whenever ulcerogenic tumor is verified.

3. A clinical example of fulminating ulcer diathesis in the absence of an ulcerogenic tumor but with possible hyperplasia of the islet tissue is presented.

4. Careful search of the pancreas should be made in all persons operated upon for peptic ulcer, especially if a primary jejunal ulcer is present.

5. Although the role of the non-beta islet cell adenoma is postulated, both the cell type and active principle must be identified to confirm or deny the relationship between these tumors and gastric hypersecretion.

DISCUSSION

JOHN J. BYRNE (Boston, Mass.): We appreciate Dr. Zollinger's very brilliant discussion and also the slides. Does anyone have any comments or questions for Dr. Zollinger? Dr. Osborne, you have had a few such cases recently, haven't you?

M. P. OSBORNE (Boston, Mass.): We have reviewed the pathological material from this hospital without actually finding any convincing case, but we have one seemingly good example from the Faulkner Hospital.

DR. BYRNE: I think there is one case in every surgeon's experience that makes him wish he had known about these pancreatic tumors ten or fifteen years ago. Occasionally we have all seen patients with peptic ulcer who ultimately required total gastrectomy before the symptoms could be brought under control. Perhaps these are examples of ulcerogenic pancreatic tumor.

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Surgery and the Thymus

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ABOUT 300 years ago deDiemerbroeck [1] wrote of the thymus in his famous anatomy of human bodies: "To this same mediastinum grows the thymus . . . a glandulous, soft, spongy and whitish body bigger in women and in new born infants than in men; in people grown it is much thinner. Wharton allows the thymus nerves . . . Harvey found chylous or milky juice there, which juice is brought to more perfection there and so transferred to the hollow vein. There are no visible nerves but perhaps there are some invisible ones to bring about some private effervescence for its own nourishment."

Even as deDiemerbroeck, Wharton and Harvey were fascinated three centuries ago by some "private effervescence" of the thymus, so too have many investigators during the intervening years tried to fathom the essential activity of this gland. In both man and laboratory animal the thymus has been extirpated, extracted, radiated, macerated and implanted to study its function. The results of these efforts were eloquently summarized by Chalmers [2] in a recent editorial: "This enigmatic gland . . . continues to guard the mysteries it has kept to itself for centuries."

The thymus looks like a gland, has no known exocrine function and is profoundly influenced by glands of known internal secretion. For these reasons it is generally believed to be an endocrine organ even though its function and secretion have never been identified. Its discussion therefore quite properly appears in this Symposium. However, its many features in common with lymphocytes and reticuloendothelium might equally well entitle it to a position in a program devoted to a discussion of those systems. Despite the fact that the physiological function of the thymus is still a mystery, so many clinical and laboratory observations have been made of it that it is clearly entitled to important consideration in modern medicine and surgery.

Anatomy. The thymus [3] arises primarily from the third pharyngeal pouches. Occasionally the fourth pouches also give rise to small amounts of thymic tissue. Early in its appearance the proliferating thymic bud has a narrow lumen, the walls of which are composed of several layers of cylindrical epithelium. As this proliferates the lumen disappears and epithelial sprouts invade the underlying mesenchyme. More or less simultaneously, lymphoid cells concentrate within the developing thymus. The epithelium loses its pavement like appearance and apparently becomes a reticular mesh, the interstices of which are packed with lymphocytes, often referred to as thymocytes. Somewhat later Hassall's corpuscles appear. These are believed to be derived from the reticular cells and are therefore regarded as epithelial in origin. By the end of the third month of fetal life the thymus is a well defined structure with both a cortex and medulla. As it descends from the neck into the thorax, a remnant may be left behind or it may carry with it one or more of the parathyroid glands. Thus normal or abnormal thymus in the neck or parathyroids within the thorax is embryologically explained [4,5].

At birth the thymus is a bilobed structure lying within the anterior mediastinum and above the heart. Location of this gland other than in the anterior mediastinum is rare but has been described in the left upper mediastinum, in the posterior mediastinum and even within pulmonary tissue. Such ectopia is variously estimated at from 5 to 15 per cent [6]. The blood supply of the thymus is derived from the internal mammary, and from the superior and inferior thyroid arteries. Venous drainage empties into the thyroid and left

innominate veins. Lymphatic permeation is extensive and drainage is into anterior mediastinal, sternal and tracheobronchial nodes. Thymic nerves derive chiefly from the vagus and sympathetic systems. Near puberty the thymus becomes relatively smaller although actually it weighs more than in infancy. Soffer [7] accepts the average weights of the thymus at various ages to be:

At birth	10–20 gm.
At puberty	30–40 gm.
In adults	10–20 gm.
In old age	5–10 gm.

Progressively during adult life thymic tissue is gradually replaced by fat, but even in advanced years some distinguishing thymic features persist.

Pathology. Atrophy of the thymus and its infiltration with fat is a normal process associated with aging. Rarely, instances of specific and non-specific infections of the thymus are reported. These normal and infectious processes, however, are relatively unimportant clinically in comparison to hyperplasia and neoplasia. Although the reasons for its appearance are not at all understood, hyperplasia of the thymus is not uncommon. It occurs under any circumstance in which lymphoid tissue generally enlarges. For instance hyperplasia is a regular concomitant of hyperthyroidism and subsides after the hyperactive thyroid is brought under control. In myasthenia gravis the thymus is hyperplastic in about 50 per cent of patients [8–11]. Hyperplasia may occur alone, however, without any detectable associated disease.

Although the classification of thymic tumors is confused, several groups of benign and malignant neoplasms are well recognized. The most common [12–15] neoplasm, the benign thymoma, appears to be largely a proliferative process of lymphocytes and reticular cells. Until recently these latter cells have been believed to be epithelial but recently Hubbell and Liebow [16] have produced evidence that the reticular cells are in fact lymphoendothelial. These tumors therefore closely resemble lymphomas in appearance. Neoplasms of this variety are fairly consistent in their behavior; they gradually become larger, and although they may slowly assume malignant characteristics they seldom metastasize by way of the lymphatics or blood vessels. They do, however, extend locally, spreading out over pleural surfaces to involve contiguous structures. After removal they are prone to recur locally. About 15 to 25 per cent of patients with myasthenia gravis have a thymoma of this variety [13].

Three other types of thymic neoplasms have been described; one by Lowenhaupt and Brown [17] resembles Hodgkin's disease, while another presents the appearance of seminoma of the testis. The origins of these tumors are obscure but thymic origin seems assured because occasionally Hassall's corpuscles are encountered within them. Anaplastic squamous carcinoma found in the anterior mediastinum has rarely been interpreted to be of thymic origin because of associated myasthenia. Great care, however, must be taken to differentiate these tumors from primary bronchogenic cancers invading the mediastinum or malignant degeneration of mediastinal dermoids or teratomas.

Physiology. In spite of well over 2,000 publications on the function of the thymus gland about the only substantial fact known about it is its tendency to enlarge when lymphoid tissue generally increases in size and to atrophy when lymphoid tissue shrinks. The atrophic thymus of the normal adult may rapidly increase in size after adrenalectomy, castration, hypophysectomy and partial thyroidectomy for hyperthyroidism. Atrophy generally takes place in association with steroid therapy, stress, an inadequate diet and under the influence of a variety of drugs. Whether these changes relate more to the hypophysis or to the adrenals is not known. In addition to these apparent relationships between the thymus and other endocrine glands the hemopoietic system appears to be affected in some obscure way. This is reflected in a failure of erythropoiesis in certain patients with thymic tumors. There is some evidence that a neuromuscular blocking agent can be extracted from normal thymic tissue. Furthermore extracts from the thymus of patients with myasthenia gravis appear capable of inhibiting acetylcholine synthesis. From a clinical study of deaths in children with thymic enlargement there is some evidence that death was due to paralysis of respiratory muscles by a curare-like substance. Torda and Wolff [18] have postulated a fraction in the serum of patients with myasthenia gravis which inhibits acetylcholine formation. From these fragmentary bits of evidence, many of them unsubstantiated, it can only be concluded that the physiologic func-

tions of the thymus are indeed not clearly understood.

Clinical Aspects of Thymic Enlargement. In infancy and early childhood a variety of cardiorespiratory disorders have been attributed to thymic enlargement. So popular was this belief a few decades ago that the chests of all infants were routinely x-rayed on admission. If the thymus was enlarged, it was vigorously treated by x-ray. Status thymicolymphaticus was popularly believed to be a predisposing cause in sudden death under unusual stress such as surgery. Today convictions such as these have largely been abandoned as more and more specific causes for sudden deaths in children have been discovered. About the most that can be said today is that in a few instances of patients with thymic enlargement who have died suddenly, adrenal atrophy has been demonstrated at postmortem examination. At least some of the deaths formerly attributed to thymic enlargement were in all probability due to adrenal insufficiency. The commission charged to investigate so-called thymic deaths concluded in 1931 that benign thymic enlargement does not play a specific part in sudden death [*19*].

In adult life enlargement of the thymus is usually discovered on routine roentgen examination of the chest because of signs and symptoms of a tumor in the anterior mediastinum or because a patient manifests stigmas of myasthenia gravis. Benign and malignant tumors of the thymus generally grow slowly and may reach considerable size before they are detected. Attention is often attracted to such tumors by the effects they produce in pressing upon the heart, great vessels, tracheobronchial tree or esophagus. When a thymoma has extended to contiguous structures such as the pleura, a hydrothorax may indicate its presence. Needless to say, thymoma can be clinically differentiated only with difficulty from other anterior mediastinal tumors unless myasthenia gravis complicates the picture. Nevertheless thymic origin of an anterior mediastinal tumor may be suspected when a circular, sharply defined mass is seen on a roentgenogram of the chest. If this mass lies above the cardiac shadow, it may be presumed to be a thymoma until proved otherwise.

Myasthenia gravis, a chronic disease characterized by variable degrees of weakness in a variety of voluntary muscles, is associated in well over half of patients with some abnormality of the thymus gland. Hyperplasia with prominent germinal center formation is encountered in about 50 per cent of patients with this disease while a thymoma is present in about 15 per cent. In the remaining 25 to 30 per cent an abnormality of the thymus cannot be demonstrated morphologically. This does not mean, of course, that an atrophic-appearing thymus heavily infiltrated with fat cannot be physiologically active. Although sparse the many foci of thymocytes and reticulum that remain may well be capable of endocrine activity. This relationship between thymic abnormality and myasthenia gravis is far greater than can be accounted for by chance and has given rise to the belief that the overactive thymus releases some as yet unidentified curare-like substance. Tumors, as might be expected, appear in middle life, while in patients without tumors the symptoms of myasthenia gravis generally appear a decade or two earlier. The age distribution among those with and without tumors is given by Keynes [*13*] as follows:

Age	0–9	10–19	20–29	30–39	40–44	50–59	60+
Tumors	0	0	2	19	11	13	3
No tumors	4	26	74	67	31	8	2

One of the characteristics of myasthenia gravis when associated with tumor is its severity, its more rapid course and the greater difficulty with which it is controlled.

Recently a relationship, again greater than chance, has been demonstrated between a peculiar form of agenesis of erythrocytes and thymoma [*20–24*]. Since this syndrome was first described by Matras and Priesel [*21*] in 1928, some fourteen cases have been recorded in detail. Characteristically the hematologic picture is one of agenesis of erythrocytes, normal platelets, normal myelopoiesis and a great reduction in reticulocytes. In several of these reported patients myasthenia gravis was also present. About half are reported to experience complete relief of their anemia after thymectomy, while in the remainder their anemia remained unchanged. This apparent relationship between the thymus and erythropoiesis is not understood [*2*].

Treatment of Tumors of the Thymus. Both benign and malignant tumors of the thymus grow slowly and for long periods of time are easily accommodated in the spacious anterior mediastinum. Since x-ray therapy is merely

palliative, all tumors of the thymus should be explored and if at all possible removed. Surgical extirpation offers the only chance of cure.

Thymectomy in Myasthenia Gravis. That a relationship might exist between the normal or hyperplastic thymus and myasthenia gravis was suspected by Wiegert [*25*] in 1901 and proved much later by Pierchalla [*26*] in 1921. The latter investigator noted that after radiation of the thymus patients with myasthenia gravis improved. This observation, substantiated by Mella [*27*] a few years later, was lost sight of until 1936 when Blalock et al. [*28*] reported startling improvement in a patient with this disease whose thymus was removed surgically. This report initiated a wave of enthusiasm in this country and in England for removal of the thymus in patients with myasthenia gravis. As experience has been acquired and greater insight achieved into the many problems involved, the original enthusiasm of twenty years ago has diminished somewhat. Spontaneous remission (a feature of myasthenia gravis), problems inherent in selection of patients, and the vagaries of attempting to estimate what would have happened if thymectomy had not been performed plague those trying to evaluate critically the effects of treating myasthenia gravis by thymectomy. As the numerous reports on this subject are reviewed, it appears that about one-third of patients operated upon will be dramatically improved or even cured; one-third will derive some amelioration of their symptoms; in the remaining third, removal of the thymus fails to alter the course of the myasthenia gravis. Keynes [*13*] in England is an enthusiastic exponent of thymectomy, while Eaton and Clagett [*10*] of the Mayo Clinic tend to be less encouraging. Grob and Harvey [*8*] prefer to reserve operation for those whose response to therapy has been poor and for those whose disease is so severe that the chance of a remission seems remote. Needless to say, any patient with a known or suspected thymoma should be studied preoperatively with great care to detect evidence of neuromuscular disease. Morphine, barbiturates and curare-like drugs should be studiously avoided preoperatively, during operation and in the immediate postoperative course. During operation neostigmine should be given continuously by the intravenous route. This should be continued postoperatively until it is assured that an acute myasthenic crisis is not going to develop [*29*].

SUMMARY

Because the function of the thymus is not understood, treatment of its diseases today continues to be empirical. Tumors, cysts and ectopic thymic tissue constitute the major problem of purely surgical significance. Among patients with myasthenia gravis the thymus is involved in hyperplasia or tumor formation in a sufficiently large number of cases to warrant thymectomy. The best results can be anticipated when operation is undertaken early in the course of the disease. An as yet unexplained relationship between the thymus and a rare form of agenesis of erythrocytes is being recognized with increasing frequency.

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DISCUSSION

DR. CHILD: Hoping perhaps to arouse further interest in the surgery of the thymus, Dr. Byrne has given me permission to show a film on this subject. This film outlines thymectomy in two patients. The first is a young woman whose left upper mediastinal mass defied accurate diagnosis until operation. It proved to be a hyperplastic gland of about four times normal size without any associated evidence of myasthenia before, during or after operation.

The second patient was a middle-aged man who indeed had a discouraging postoperative course. Because of signs and symptoms of pulmonary sepsis, increasing dyspnea and precordial pain he, at one time or another, was thought to have bronchiectasis, pulmonary fibrosis and myocardial infarction. Several months before I first saw him a mediastinal mass was discovered on roentgen examination of the chest. The thorax was explored without a positive preoperative diagnosis. I am embarrassed to say that thymoma was not considered. During the operation acute signs of myasthenia gravis developed. Although he survived for ten days after removal of a large malignant thymoma, he suddenly died in an acute myasthenic crisis.

These two patients are individuals from whom I have learned a number of lessons—not, I assure, you from positive achievements.*

QUESTION: Are there any precautions which should be taken during or after operation on a patient suspected of having myasthenia gravis?

DR. CHILD: I believe that any patient with a mediastinal tumor which is even remotely suspected of being a thymoma, or any patient known to have myasthenia should be protected throughout the operation and postoperative course by the intravenous administration of prostigmin.® Furthermore, barbiturates, morphine and, most particularly, curare-like drugs should be avoided.

QUESTION: What caused your second patient's death ten days after operation?

DR. CHILD: Acute respiratory failure which did not respond to even massive doses of prostigmin. He went into a so-called myasthenic crisis.

QUESTION: Dr. Child, would you be willing to commit yourself as to which patients you would select for surgery as against medical treatment?

DR. CHILD: This a difficult question to answer precisely. I believe that among patients with myasthenia but without evident tumor I should operate upon those whose muscle weakness can barely be controlled by even large doses of prostigmin. I should also be inclined to operate upon patients whose course has indicated very little possibility of a spontaneous remission.

QUESTION: Do you mean you would be selective among patients with myasthenia?

DR. CHILD: Yes.

QUESTION: What about patients with demonstrable tumor?

DR. CHILD: All patients with thymoma should; of course, be operated upon. The real problem patient is the woman without a tumor who develops myasthenia in her middle twenties or thirties and whose symptoms are easily controlled by small doses of prostigmin. In such patients the greatest controversy centers around our inability to predict which patients will benefit from thymectomy and which patients will not. If such a patient is operated upon and has a remission, it is awfully difficult to say what might have happened had she not undergone surgery. This is a very difficult problem to which there is no really satisfactory answer today.

* At this point in the discussion a short colored motion picture was shown.

Carotid Body and Allied Tumors

JOHN J. BYRNE, M.D.,* *Boston, Massachusetts*

SINCE the carotid body was first discovered by Von Haller (1743), it has been the subject of much investigation and conjecture. Considering the rarity of the lesion, the literature has been immense. As long ago as 1917, when reporting one of his cases, Lund [*1*] had this to say: " . . . and these curious little tumors have been dissected, studied and described almost ad nauseam et ad infinitum." One wonders what he would say today. The rarity of the lesion is emphasized by the fact that the first case in which operation was performed at the Boston City Hospital was in 1887, seventy years ago. Since then, six tumors from our institution plus three cases operated upon at the Carney Hospital but studied at the Mallory Institute of Pathology form our total experience with the disease.

I. GENERAL PATTERN

The function of the carotid body is fairly well established as a chemoreceptor, but there is still a vague undercurrent of thought as to its endocrine nature, with carotid body excision being performed for myasthenia gravis and rheumatoid arthritis [*2*].

The discovery of similar structures in other parts of the body which probably have a similar function has led to the belief that they form a definite system, and tumors arising from this system have been called *chemodectomas* [*3*].

Histology

These bodies consist of sheaths, cords or clusters (Zellballen) of epithelioid cells of two general types. The most common is a polyhedral cell with fine granular cytoplasm and large vesicular, pale-staining, round or oval nuclei. (Fig. 1.) The infrequent type exhibits an eccentric, deeply staining nucleus. These cells do not give a true chromaffin reaction. However, an apparent chromaffin reaction may take place due to lipoid substances in the cells (De Castro [*4*]) or mitochondria (Hollinshead [*5*]). Hollinshead also found a rich distribution of fuchsinophilic granules within the cytoplasm which stain with supravital neutral red, but not with Janus green, indicating that the majority are not mitochondria. No fat, glycogen or cholesterol could be found. The granules have not given a peroxidase reaction and their chemical composition is unknown. Hollinshead believes they must play a role in the initiation of chemoreceptor reflexes, but their precise nature is obscure.

The stroma is an extensive fine network of reticulin fibers, between which are innumerable capillaries. The capillary network is so rich that it has been thought to resemble a glomerulus and that this body is an organ of internal secretion. However, there is a definite layer of hyalin between the capillaries and the parenchymal cells. The capillaries are lined by a hyperplastic endothelium. A nerve supply is found with the terminal arborizations ramifying about the parenchymal cells.

Embryology

What is the origin of the carotid and allied bodies? Although definite opinions have been stated by numerous investigators, there is still much that is controversial [*6*]. Apparently there are a series of epithelioneural bodies in animals. The first group are the *neuroectodermal organs* or true paraganglions which derive from the neural crest. In this group may be placed the medullary zone of the adrenal gland, the organ of Zuckerkandl at the origin of the inferior mesenteric artery, and other bodies along the aorta. These give a true chromaffin reaction. It is to be emphasized that this chromaffin reaction is not a true test of paraganglions, since

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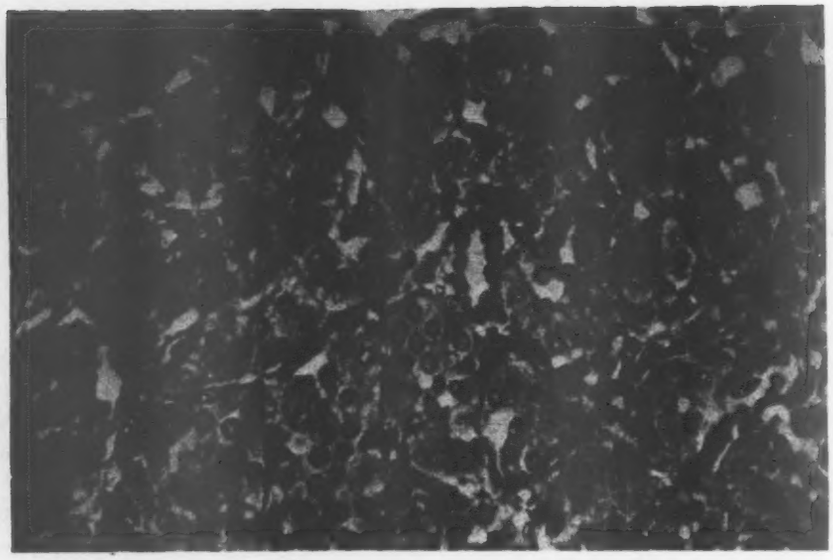

FIG. 1. Normal carotid body showing clusters of polyhedral cells in a network of reticulin fibers and capillaries.

Kulchitsky's cells, which are definite intestinal epithelial cells, give a strong reaction, and irregular reactions are found in the adrenal medulla.

A second group of organs has the epithelial component originating from the embryonic *endoderm*. These become argentaffin only on migration into the local nerves, with this reaction disappearing as the cell migrates farther from the tips of the glands. The cells look like typical ganglion cells and are present in the pancreas, liver, appendix and duodenum.

A third and very rare group are those in which the epithelial cells derive from *mesoblastic origin* in the region of the rete testis, albuginea of the testis, along the spermatic cord, in the hilus of the ovary and in the broad ligament. These are Berger's so-called sympathicotrope cells.

The epithelial cells of the glomus and coccygeal bodies derive from *smooth muscle* cells and are probably contractile in function.

Where do the carotid and allied bodies fit into this scheme? The carotid body arises as a condensation of the mesodermal cells in the wall of the third arch artery above the origin of the external carotid artery. (Fig. 2.) The cells of this condensation are in direct contact with the cells forming the media and adventitia but can be distinguished from them by their oval or polyhedral shape and their oval nuclei poor in chromatin. (Fig. 3.) Smaller cells with nuclei rich in chromatin also are seen.

Most investigators appear secure in the belief that the cells of the pharynx play no role in this development. This leaves us then with the mesoblastic and neural origins.

Kohn [7] in 1900 first believed that these were of neural crest origin and classified them as paraganglions of the non-chromaffin type. Other investigators since have similarly thought that they originate from nerve tissue. Benoit [8] was of the opinion that they came from the ganglion nodosum of the vagus nerve and migrated into the third aortic arch, and that all the embryonic aortic arches are endowed similarly with cuffs of neural cells from anlagen of other cranial nerves and ganglia. Winiwarter [9] believed they came from the petrous ganglion of the glossopharyngeal nerve. On the other hand, Boyd [10], in his classic work at the Carnegie Institute (1937), believed that the aortic pulmonary bodies were of mesenchymal origin and related to the fourth and sixth arches, whereas the carotid body was of similar mesenchymal origin related to the third arch.

Hammond [11] studied the aortic arch bodies and believes that they are derived mainly from vagal cells which migrate along the depressor nerves. The mesenchyme plays no significant role in the formation of these bodies. He believes they are definite neural epithelial cells and are similar to the taste buds of the tongue and rods of the retina.

Barrett [12], of the Anatomy Department of Boston University, states: "It would seem that

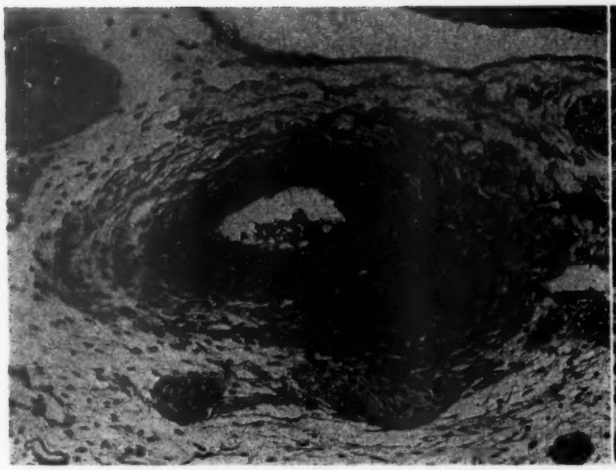

FIG. 2. Carotid body arising as a condensation of cells in the wall of the internal carotid artery. (From the embryology collection of Dr. Elizabeth K. Moyer, Associate Professor of Anatomy, Boston University School of Medicine).

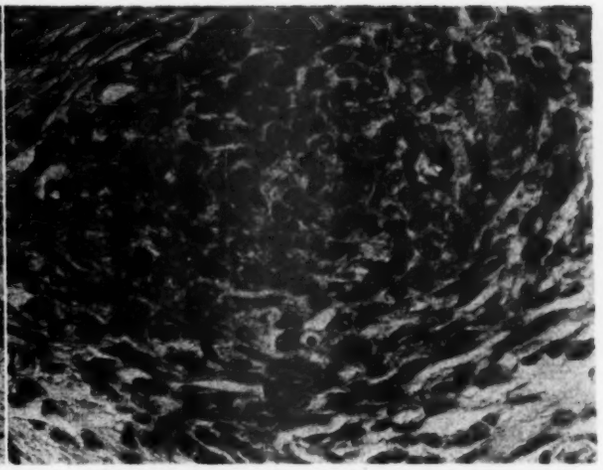

FIG. 3. Higher magnification of developing carotid body seen in Figure 2.

the carotid body is composed of epitheliod cells derived from periarterial mesenchyme cells as well as neural elements derived by migration of cells from the petrosal ganglion of the glossopharyngeal nerve and possibly from the vagal ganglia. Although other cellular elements may enter into the formation of this structure their contribution is small and their fate uncertain."

Function

The similarity of these organs to secreting glands has suggested that they play an endocrine role. However, there is a paucity of evidence for this, the latest being the work of Christie [*13*], who has isolated material from a carotid body tumor which produced a drop in blood pressure and an increase in heart rate, and whose action was unaffected by atropine. However, the majority of investigators are fairly definite that there is no secretory function.

In 1928, on the basis of its peculiar histologic appearance, De Castro [*4*] suggested that it might represent a special sense organ capable of perceiving changes in the chemical composition of the arterial blood. This was confirmed by the classic work of Heymans et al. [*14*] in 1930 and subsequently amplified by many investigators [*15–18*].

The stimuli for this chemoreceptor are numerous and include a decrease in arterial oxygen tension, an increase in blood acidity, in carbon dioxide tension of the blood and in blood temperature. In addition, there are certain drugs which have a stimulating effect. These include sulfides, nicotine, lobeline and papaverine. Also, certain drugs which inhibit oxygen consumption (sodium azide, cyanide, 2,4-dinitrophenol) and certain energy-rich phosphates (adenosinemonophosphate, adenosinetriphosphate, pyrophosphate) stimulate the gland. There are a few agents which have an opposite effect: uncouplers of oxidative phosphorylation (thiopental, pentobarbital) and glucose and sodium salts of succinic, acetic and pyruvic acid. The response to these stimuli is essentially trifold, consisting of an increase in respiratory rate, depth and minute volume; increase in sympathetic nervous activity manifested by tachycardia, increased blood pressure, increased vasoconstrictor tone and the liberation of adrenalin, and an increase in cerebral cortical activity. The latter may explain the restlessness of anoxia. This response can be maintained for long periods.

Extirpation and denervation of the carotid bodies produce no lasting change in the respiration or circulation. It has been proved fairly conclusively that the gland does not secrete epinephrine.

Daly et al. [*19*] investigated the blood flow of this gland and found the average carotid body blood flow to be 38 cu. mm./minute. This is dependent on the level of the blood pressure going through it. Electrical stimulation of the sympathetic nervous system controlling this gland reduces the carotid body blood flow. There is an appreciable metabolic use of oxygen by the gland. They present evidence that the carotid body can be stimulated by intrinsic

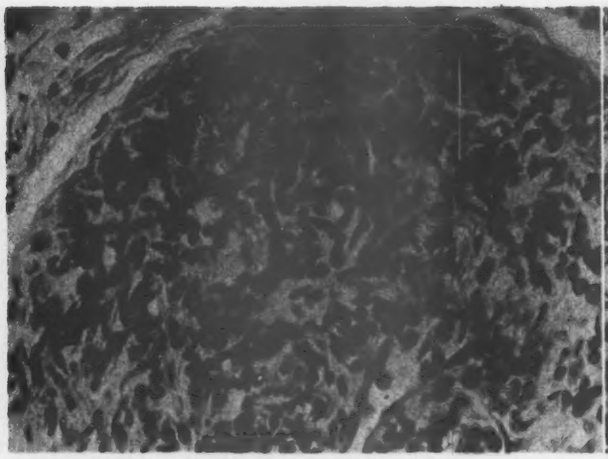

FIG. 4. Carotid body tumor; nests of polyhedral cells arranged in clumps.

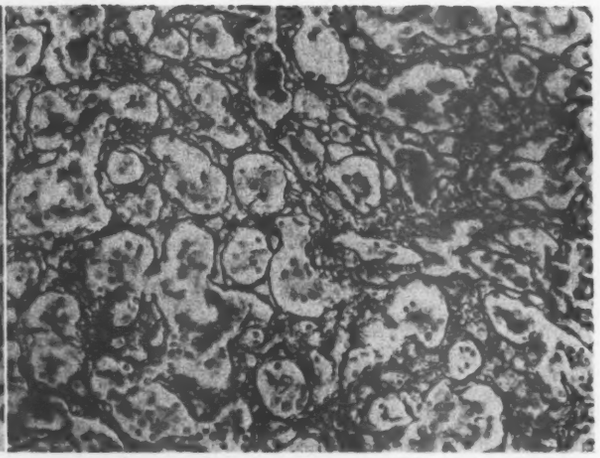

FIG. 5. Carotid body tumor; special reticulin stains demonstrate Zellballen architecture.

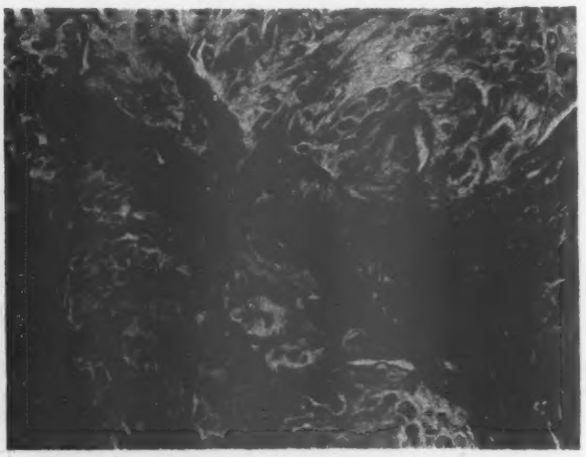

FIG. 6. Carotid body tumor; hyalinization of connective tissue may be a prominent feature.

anoxemia of the gland in the presence of normal arterial oxygen tension. Occlusion of the carotid arteries causes an increase in respiration, and the same occurred with bleeding in addition to a reflex rise in arterial blood pressure. Thus the blood pressure of the carotid body itself affects the blood pressure of the body.

Tumor Histology

The characteristics of the tumor are essentially the same as those of a normal gland. Sheets or cords of polyhedral epithelial cells with finely granular cytoplasm and pale staining, large, round or oval nuclei may be seen. (Fig. 4.) Occasionally one sees the small darker cells with eccentric nuclei. These cells may be arranged in clumps (Zellballen), and at times a special reticulin stain will be necessary to bring out this appearance. (Fig. 5.)

The stroma consists of fibroblastic fibrous tissue and capillaries, and is well emphasized by reticulin stains. Hyalinization of the connective tissue may be a prominent feature. (Fig. 6.)

Le Compte [20] emphasizes several other variants of this normal pattern. One is the adenoma-like pattern with pronounced epithelial appearance, scanty stroma and an alveolar arrangement of the cells. The other is an angiomatous pattern where the vascular elements are profuse, the cells smaller and less prominent, and crescentic or spindle shaped. (Fig. 7.)

Mitoses and bizarre forms are rare, and the usual histologic criteria of malignancy are missing. (Fig. 8.)

Although these tumors grow locally and encase surrounding structures (such as the vagus nerve, jugular vein, hypoglossal and glossopharyngeal nerves), the media of the carotid artery is not invaded; and this is important from the point of view of surgical treatment.

Spread of Tumors

The low grade of malignancy of these tumors is emphasized by many investigators. On the basis of this, conservative therapy has been advocated whenever it seems necessary to ligate the carotid artery. However, the problem is not as simple as this; and although the malignancy rate is relatively low, there are numerous cases of definite malignancy as evidenced by all methods of spread.

The majority are benign indolent growths

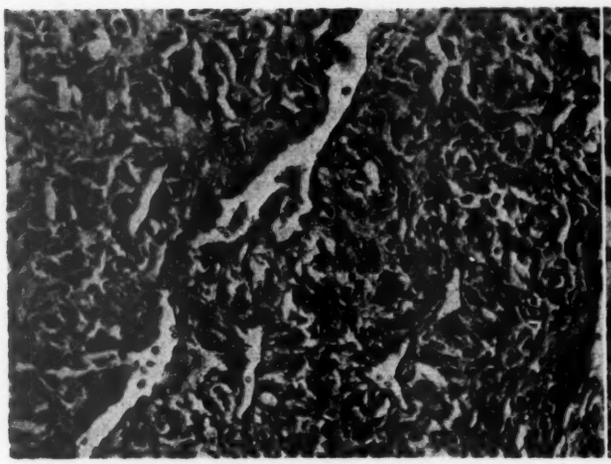

FIG. 7. Carotid body tumor; angiomatous pattern with prominent vascular elements.

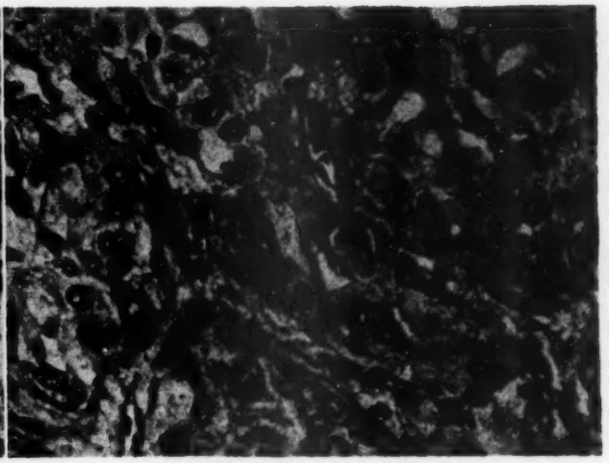

FIG. 8. Carotid body tumor with bizarre shapes and sizes of cells.

which are often present for years and tend to expand and incorporate adjacent structures rather than infiltrate them. Many patients die from local tumor recurrence. Morfit et al. [*21*] found seven cases in the literature, and other cases are reported. MacComb [*22*] reports recurrence after resection of a carotid artery; this patient died at home two years later with a mass in the neck and bilateral nodes involving the base of the skull. To this case may be added the case of Arean [*23*] in which there were two recurrences over a five-year period where the tumor had extended into the spinal canal. The patient eventually died with a thrombosis of the carotid artery following dissection of the tumor, and it was found that the tumor had dissected into the spinal canal.

Spread to adjacent lymph glands is also relatively rare, but numerous authenticated cases have appeared [*21–28*].

Definite blood stream metastases have been similarly reported. This problem is complicated however by the tendency for these tumors to have a multicentric origin: simultaneous carotid and jugular [*29–31*]; carotid, aortic and vagal [*32*]; carotid and vagal [*32*]; carotid and ciliary [*33*]. Nevertheless, definite blood-borne metastases have occurred to bones, lungs, heart, pancreas and kidney [*21–28,34–39*].

II. INDIVIDUAL TUMORS

Ciliary Body

A group of cells has been found in the ciliary ganglion of the chimpanzee by Botar and Pribek [*40*].

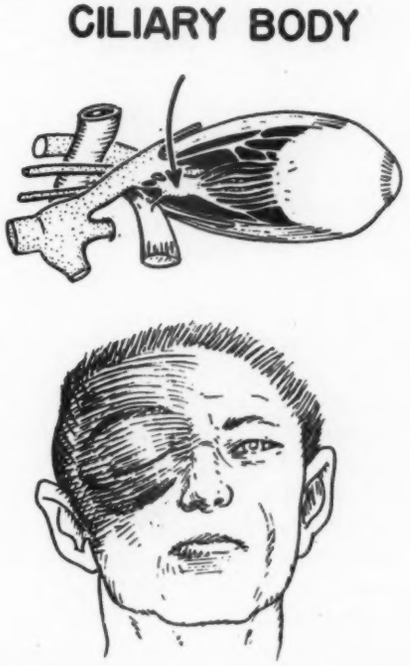

FIG. 9. Chemodectoma of ciliary body. First described (in chimpanzee) by Botar and Pribek [*40*] in 1935; tumors described by Fisher and Hazard [*41*] in 1952 and by Lattes, McDonald and Sproul [*33*] in 1954.

Two cases of tumors of this system in humans have been reported by Fisher and Hazard [*41*] and by Lattes et al. [*33*].

There is usually a bulging of the eye with loss of vision, and a mass may extend into the right temporal region. (Fig. 9.) Treatment is extirpation with exenteration of the orbit.

Jugular Body

The jugular body was first described by Valentin [*42*] in 1840 as the so-called gangliolum

tympanicum. It was rediscovered by Guild [43] in 1941.

This is a single, sometimes lobulated, occasionally multiple structure situated in the dome of the jugular bulb immediately beneath the bony floor of the middle ear near the ramus

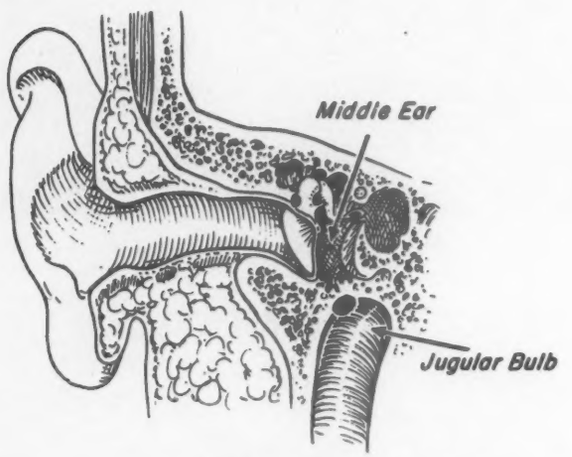

FIG. 10. Jugular body. First described by Valentin [42] in 1840; first tumor described by Rosenwasser [44] in 1945; over seventy cases reported to date.

tympanicus of the ninth cranial nerve (Jacobson's nerve). (Fig. 10.) Rosenwasser [44] described the first tumor of this body, and since then a review of pathological slides of previously reported and additional cases have brought the total to over seventy [45,46].

There is usually tinnitus, progressive deafness, occasional vertigo with otorrhea, chronic otitis media and hemorrhage from the ear. Facial paralysis has been reported.

Local examination reveals the otic membrane to be red and bulging. A friable polypoid mass often grows along the external canal or presses on the drum. It may bleed profusely on biopsy or attempted removal. This tumor invades the middle ear with destruction of the petrous portion of the temporal bone. Occasionally the x-ray appearance may simulate chronic sclerosing mastoiditis.

Treatment is radical resection through the mastoid approach. Occasionally the symptoms resemble a cerebellopontine lesion, and one was reported which was explored intracranially [47].

Aortic Pulmonary Body

These were first described by Biedl and Wiesel [48] in 1902, and to date five tumors have been ascribed to it [32,49,50]. These are numerous bodies which appear in relation to the great vessels of the heart. (Fig. 11.) One is fairly constant near the innominate artery either at its bifurcation or lateral to the origin of the subclavian, and another is present on the

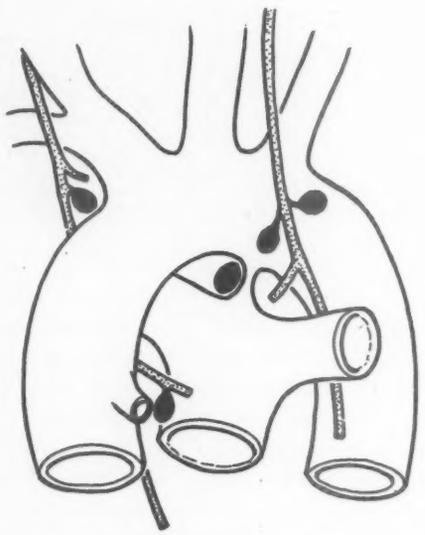

FIG. 11. Aortic bodies. First described by Biedl and Wiesel [48] in 1902. Five tumors reported to date: two tumors, Duncan and McDonald [49] in 1951; two tumors, Lattes [32] in 1950; one tumor, MacDonald [50] in 1956.

anterolateral aspect of the left portion of the aortic arch near the origin of the left subclavian. One is found near the ductus arteriosus. The afferent nerve supply of these is from the vagus nerve. They are usually asymptomatic, but one case of Lattes presented as a supraclavicular growth.

Vagal Body

This was first described by White [51] in 1935. To date, five tumors have been reported [34,46]. This body can be found within or without the perineurium of the vagus nerve enclosed within the substance of, or upon, the surface of the nerve at the level of the ganglion nodosum just below the ganglion or scattered in tiny bundles throughout the ganglion. (Fig. 12.)

There is usually a painless swelling of long duration above and behind the angle of the mandible between that bone and the mastoid process. It may press on the oropharyngeal wall and interfere with swallowing, or may involve the lower four cranial nerves resulting in

hemiatrophy of the tongue, vocal cord palsy, atrophy of the sternocleidomastoid and trapezius muscles.

Treatment is total extirpation, and partial removal of the mastoid process may be helpful.

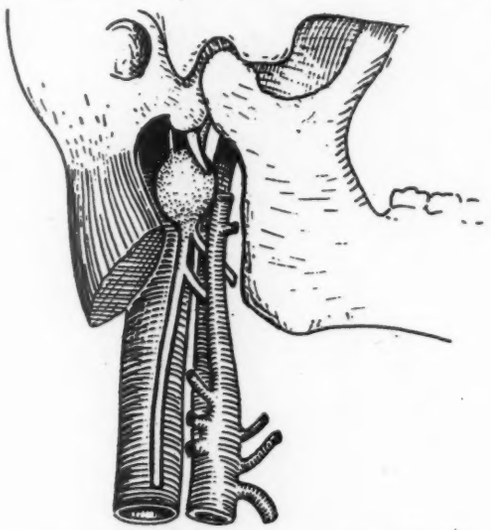

FIG. 12. Vagal body. First described by White [*51*] in 1935; tumor first described by Stout in 1935; five cases reported to date.

Alveolar Body

Although no definite alveolar body has been found as yet, chemodectoma of the mandible has been described [*46*].

Femoral Body

Eight tumors thought to have their origin in this system have been found in the thigh between Poupart's ligament and the popliteal fossa, usually in the vicinity of the vessels within or about Hunter's canal [*52*]. (Fig. 13.) These neoplasms were situated in the deeper layers of the thigh closely associated with striated muscle or fascia. There were usually mild symptoms with a noticeable tumor which frequently was slightly tender or painful. In five of the cases there were metastases to lung, brain, bone and lymph nodes. Two cases were lost to follow-up. Randall and Walter [*38*] report a similar case in a twenty-two year old woman which did not respond to x-ray and metastasized to the right lower lobe of the lung. The tumor of the thigh was excised together with the right lower lobe of the lung and the tumor definitely identified. Two years later the patient was still alive but metastases were present in the left lung.

These tumors resemble granular cell myoblastomas only in the granularity of their cytoplasm, and it was the belief of both pathologists that the tumors were allied to the carotid bodies.

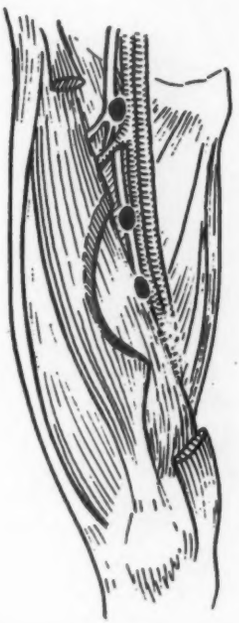

FIG. 13. Femoral bodies. Nine tumors reported to date: eight tumors, Smetana and Scott [*52*] in 1951; one tumor, Randall and Walter [*38*] in 1954.

Retroperitoneal Body

Four tumors in the retroperitoneal area and one in the mesentery of the ileum have been reported [*52,53*]. The histology was similar to the carotid body tumor. Two metastasized: one to the lungs and adrenal, and one to the lungs and brain.

Carotid Body

In 1880 Riegner removed the first tumor ascribed to the carotid body, and in doing so had to excise the carotid artery, jugular vein, vagus, hypoglossal and sympathetic nerves; the patient died on the third postoperative day. In 1886 Maydl operated upon the second patient, performing resection of the bifurcation of the carotid with resultant hemiplegia, facial paralysis and aphasia, with recovery. In 1889 Albert operated upon the first patient without ligation of the carotid. Scudder [*54*] in 1903 resected the first verified American case, with

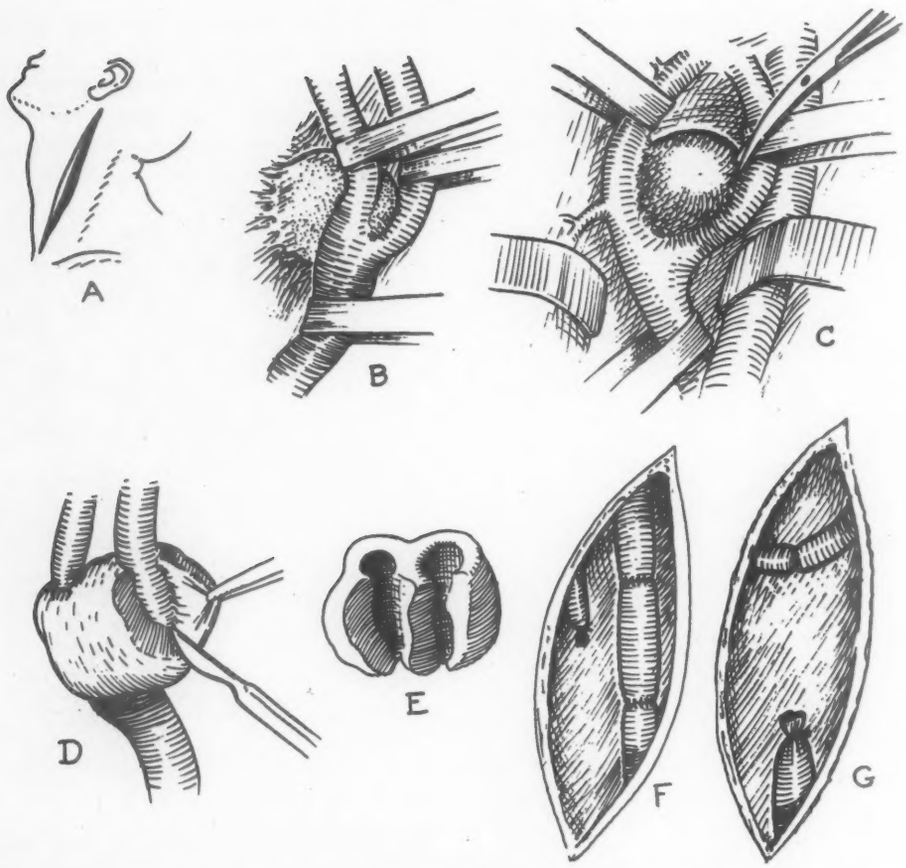

FIG. 14. Carotid body tumor. A, usual incision for removal of this tumor. B, control of common, external and internal carotid arteries with tapes. C, tumor dissected from bifurcation. D and E, tumor may be longitudinally incised and carefully dissected from arterial media. F, artery graft may replace resected bifurcation. G, anastomosis of internal and external carotid arteries.

recovery. Since then the list of tumor cases has grown to over 300 [*46,55,56*].

The carotid body is a soft, ovoid or irregular, tough, pale tan structure (measuring about 5 by 3 by 2 mm.) usually resting against the medial aspect of the common carotid artery at its bifurcation in the loose areolar tissue but firmly bound to the vessels. It may be absent on one or both sides. It is somewhat oblong, with its greatest axis vertical and connected to the carotid bifurcation by a fibrovascular band, the ligament of Mayer.

The body is surrounded by a thin fibrous capsule from which connective tissue penetrates the gland and forms septa, dividing it into lobules. In these septa the blood and nerve supply enter the gland. At the age of twenty or thirty the fibrous stroma increases at the expense of the parenchyma.

The arterial supply is from the carotid bifurcation, most often from the external carotid artery through the ligament of Mayer. The veins empty into the superior laryngeal, lingual and pharyngeal veins, and leave at the upper pole. It receives its nerve supply from the branch of the glossopharyngeal nerve.

Carotid body tumors are slow growing, usually painless tumors, arising in the upper superior cervical triangle and pushing out the anterior border of the sternocleidomastoid muscle. (Fig. 14.) They are usually unilateral, but bilateral involvement has been reported. They are ovoid, elastic, deep seated and not attached to skin. A bruit or thrill may be heard or felt, and transmitted pulsation from the carotid arteries often is confused with a carotid aneurysm. Compression of the carotid artery below the tumor may diminish its size, and pressure on the tumor itself may reduce its size due to its vascularity. There is lateral

but no vertical mobility. It is about the only tumor in this region on which a large vessel can be felt pulsating over it.

It may press on various nerves: the vagus to produce vocal cord palsy, the sympathetic to produce Horner's syndrome, the hypoglossal to produce hemiatrophy of the tongue, and the spinal accessory to produce paralysis of the trapezius and sternocleidomastoid muscles. Vague abdominal complaints occasionally have been reported due to pressure on the vagus nerve. The carotid sinus occasionally may be sensitive to a mass pressing on it, so that a few will present symptoms of the carotid sinus syndrome. Three of thirteen patients exhibited this symptom [*57*].

It is usually a disease of middle age, but tumors have been found in patients ranging from six months to eighty years of age.

Occasionally there is a familial tendency. Lahey and Warren [*27*] reported tumors in three siblings in one family, and two other members of the same family had excision of the tumors by other surgeons. Chase [*58*] reports two cases occurring in sisters.

The differential diagnosis includes branchial cyst, aberrant thyroid, neoplasm or infection of lymph glands or aneurysm. Recently a giant cell arteritis was reported in which the bifurcation of the carotid was occupied by a firm smooth mass about 4 cm. in diameter [*59*]. There was no cleavage plane between it and the vessels. This seemed to be a characteristic carotid body tumor, and after several partial occlusions of the carotid artery the bifurcation of the carotid with the tumor was excised. Microscopic examination revealed connective tissue with inflammation in which large multinuclear foreign body giant cells were noted in the tissues surrounding the vessels. This is a rare disease entity in which the patient complains of weakness, anorexia and weight loss associated with anemia and mild leukocytosis. There may be pain in the teeth, ear, jaw, zygoma, neck or back of the skull. Headaches may be present over the distribution of the temporal arteries. About 70 per cent of the patients have an inconstant, low grade fever, and pain on mastication is present in about 50 per cent of the cases. Death occurs in a little under 20 per cent of the cases, often due to carotid artery involvement.

Occasionally angiography may be of value [*60*]. In such cases one can see a dense network of vessels branching from the carotid arteries. The larger vessels are displaced laterally.

Surgical removal has proved to be the most efficacious mode of therapy, since x-ray in most cases is of little value. However, it must be emphasized that occasionally a carotid body tumor will respond to therapy and it may be worthwhile in inoperable cases. Doermann and Meffley [*61*] recorded a large carotid body tumor which was treated with 3,400 roentgen units followed by regression of the tumor—at least a temporary regression.

Surgical removal requires wide exposure using a longitudinal incision in line with the sternocleidomastoid muscle. (Fig. 14A.) This muscle, the jugular vein and the vagus nerve are retracted laterally and the tumor exposed. The common carotid artery is dissected at the level of the clavicle, the internal and external carotid arteries are dissected above the tumor, and tapes are placed around them to aid in hemostasis and further dissection. (Fig. 14B.) The tumor is freed from the pharyngeal wall and further dissection is continued, with care taken to avoid damage to the hypoglossal nerve and sympathetic chain. If possible, the tumor is then dissected from the bifurcation (Fig. 14C) and, if necessary, a subadventitial dissection can be performed. This plane may be delineated by the use of a procaine infiltration. With care, most tumors can be dissected free of the bifurcation and, if necessary, the tumor can be incised longitudinally down to the artery and then removed [*62*].

If it becomes evident that dissection of the tumor from the bifurcation is not possible, *what then should be done?* In the past one either had the choice of doing an excision of the bifurcation or leaving the tumor alone, taking a chance on spread of the tumor by local growth, lymph glands or blood stream. The common carotid artery ligation is swamped with difficulty, with an approximate mortality rate of 30 per cent. Many efforts have been made in the past to circumvent this. The preoperative ability to withstand digital compression of the common carotid artery for ten minutes has been suggested as a reliable guide that a patient could tolerate excision of the carotid bifurcation. However, this has not proved infallible and patients have died who could withstand such compression. Another suggestion was repeated compressions of the carotid vessels to improve the collateral circulation. Unfortu-

nately, this improves only the collateral circulation of the external carotid which is destroyed with the bifurcation removal. Sweet et al. [*63*] studied this problem after clipping of the common carotid artery, and demonstrated that the initial fall in blood pressure was fully maintained despite any possible increase in collateral circulation which may have developed intracranially as long as five weeks after common carotid obstruction.

Many people believe that younger patients can withstand ligation better than those in the older age group, but there have been reports of deaths at the age of thirty-one, and following bifurcation excision in a patient twenty-four years of age [*57,64*].

Conley and Pack [*65*] had an experience with a procedure first devised by Erlander (1937). If they resect the bifurcation, they carefully anastomose the external to the internal carotid arteries and have had success with this procedure. (Fig. 14G.) This raises the question of whether one can obtain a collateral circulation in this manner. Sweet and Bennett [*66*] checked the retrograde flow of blood from the external to the internal carotid and demonstrated variable results. In other words, in some cases, any blood supply coming through the circle of Willis may be short-circuited down the internal carotid through the external carotid. However, it was of interest that: "The two patients in the series of thirty-nine who have the largest backflow from the external carotid artery were in the sorest need of it, whereas the four patients in whom blood drained from the brain to supply the face when the external carotid was opened still had a substantial safe level of pressure in the internal carotid."

Some investigators believe that anticoagulants are of value after bifurcation removal in view of the fact that there is an extremely long segment of artery with no branches from the bifurcation to the circle of Willis, a distance of approximately 17 cm. [*57*]. This blind segment could easily thrombose, and they report four cases of anticoagulant therapy with no deaths. Although this is not advised as a routine procedure, it would seem that whenever the bifurcation is excised, anticoagulant therapy should be attempted.

If during the dissection of the tumor it is found to be attached to a small portion of the common carotid artery, it certainly would be feasible to excise this portion of artery and perform an anastomosis. If this is impossible and it is deemed necessary to go ahead with the procedure because of serious symptoms such as dysphagia or undeniable malignancy, the bifurcation would have to be resected; but some effort should be made to restore continuity of the vessel by either a vein or an artery graft. (Fig. 14F.)

III. EXPERIENCE IN THE BOSTON CITY HOSPITAL

The Mallory Institute of Pathology has had experience with nine of these tumors. Case I was reported by Lund [*1*] in 1917, and Case VIII was reported in detail by MacDonald [*50*] who also mentioned seven of the other cases but did not give any report.

CASE I. Mrs. S., a twenty-five year old woman, was admitted to the Boston City Hospital in 1887 complaining of a lump under the angle of the left jaw of two years' duration. This was about the size of a walnut and was believed to be connected with the artery. It was pulsating and apparently expanding. A bruit was heard over the tumor. An operation was performed by Dr. George W. Gay, described as follows:

"An incision was made in line over the carotid from the middle of the clavicle along the front of the sternomastoid up to the angle of the jaw. The carotid sheath was opened and the vessels laid bare just above the omohyoid muscles. As there was some doubt about the character of the tumor, it was thought best to expose it, hence the incision was prolonged to the apex of the mastoid and dissection was carefully carried down until the tumor was reached. It was found to be enclosed in a distinct smooth capsule and to lie beneath the carotid rising in front and behind so as to partially *embrace* it. There was considerable difficulty encountered when removing it because of its depth and intimate relation with the vessels. The tumor was found to be of an oval form the size of a large walnut and, on section, it was dark reddish brown and of fleshy consistency. The carotid was exposed bare to its sheath for a distance of about 1½ inches. There was profuse hemorrhage from the walls of the cavity. One small artery was tied and the remaining hemorrhage stopped by pressure. The edges of the wound were well approximated with a continuous catgut suture. A drainage tube was inserted at the lower end of the incision and a gauze dressing applied."

This woman subsequently came to see Dr. Lund on November 10, 1916. On the right side of the neck there was a tumor the size of a hen's egg which appeared to pulsate because the common and internal carotid artery ran over the top of the

tumor. The tumor was moveable from side-to-side but not from above downward. Part of it lay behind the upper portion of the sternomastoid and extended from the tip of the mastoid down to the top of the thyroid cartilage. The tumor was excised and resection of the bifurcation was necessary. The patient had hoarseness and difficulty in swallowing for a few days, but subsequently had good health. At this time Dr. Lund believed that this was the first patient whose tumors had been operated upon successfully on both sides of the neck.

CASE II. S. W., a fifty-four year old woman, was seen in 1921 with swelling of the right side of the neck of five years' duration. She had had four or five x-ray treatments but the tumor did not respond. There was never any pain in the tumor.

Examination revealed swelling of the neck extending from the lower border of the maxillary line back of the ear and into the neck.

At operation a tumor as large as a hen's egg was found lying back of the upper end of the sternocleidomastoid muscle extending anteriorly behind the hypoglossal nerve and posteriorly behind the sternocleidomastoid muscle into the posterior triangle. The mass was felt to be deep lying and manipulation caused coughing. It did not appear to be connected with the carotid sheath and at no time did the operator see the carotid bifurcation. It was vascular, discrete and well localized and had not infiltrated surrounding tissues. Although the glands were not involved, the neighboring glands were removed.

Dr. John Bottomley performed this operation and made the preoperative diagnosis of "dermoid" or "lipoma," and his postoperative comment was, "I never saw anything like it."

CASE III. (B. C. H. No. 41737.) E. T., a forty-five year old woman, had swelling of the right side of the neck of five years' duration. The swelling was non-tender, smooth, firm and not fluctuant. There was a noticeable transmitted pulsation along its base.

At operation a tumor the size of a "pullet egg" was lying in the bifurcation of the carotid. It was found necessary to excise the external, internal and common carotid arteries in order to excise the mass. The postoperative course was uneventful save for hoarseness.

CASE IV. Mrs. W., a sixty year old woman, was admitted to the Carney Hospital in 1928 with a four-month history of a mass in the left side of the neck. She had shooting pains above and below the area of growth. The left tonsillar fossa was pushed forward by the growth, as was the anterior cervical fascia. It appeared to be attached to the submaxillary gland. The mass was about the size of a walnut, soft and cystic in texture. At operation, the tumor was located in the region of the bifurcation of the carotid and it was carefully removed.

CASE V. This fifty-six year old woman was admitted to the Carney Hospital in 1934 with a mass in the right side of the neck of five years' duration, which had started to enlarge one month before admission. There were no other symptoms. On the right side of the neck a firm, non-tender, non-movable mass the size of a half dollar was felt on the angle of the right mandible. No palpable glands were felt.

Operation revealed the tumor to be located in the upper part of the superior carotid triangle and extending into the digastric triangle and beneath the angle of the jaw. It lay between the internal and external carotid arteries. Ligation of the external carotid was done to control bleeding. The tumor ran close to the jugular foramen and was about the size of a walnut.

CASE VI. (B. C. H. No. 1293428.) In 1948 this woman was admitted to the hospital with a lemon-sized mass in the left side of the neck of about six years' duration. It was not fixed to the skin or superficial structures. It was non-tender, not fluctuant and there was no venous distention. X-ray examination revealed minimal arthritis of the lower cervical vertebra.

At operation the mass (4 by 2 by 3 cm.) was carefully dissected from the bifurcation of the carotids and all the tumor was removed.

The patient subsequently returned to the hospital and died in 1956. At postmortem examination there was no evidence of recurrence.

CASE VII. (B. C. H. No. 1477992.) L. L., a thirty-four year old man, entered the hospital in 1953 with a mass in the left side of the neck of one year's duration. There had been a slight enlargement over this period, associated with sharp pain behind the ear.

A 5 cm. smooth, tender mass was present in the upper part of the left side of the neck anterior to the sternocleidomastoid muscles fixed to deep structures. The pulse was transmitted slightly.

At operation the mass was dissected from the junction of the external and internal carotid arteries. It was necessary to ligate the lingual artery. The patient had a normal postoperative course.

CASE VIII. (B. C. H. No. 1556548.) M. C., a seventy-nine year old man, was admitted to the hospital in 1955 with massive hematemesis and melena. He died within minutes of arrival. This case had been previously reported by MacDonald.

Postmortem examination revealed the cause of death to be ruptured esophageal varices. An incidental finding was an unusual mass on the left subclavian artery. It was located immediately distal to the thyrocervical axis and completely encircled the left subclavian artery without significantly narrowing its lumen. No connection with the carotid artery or the vagus nerve was demonstrated. The tumor was oval, very firm and had a fibrous encapsulation. Histologic section showed that it resembled a carotid body tumor. It proved to be an aortic body tumor.

CASE IX. (B. C. H. No. 15664191.) A. G., a fifty year old woman, came to the hospital in 1956 with a lump on the left side of the neck of six years' duration. Two years before admission she had been operated upon at another hospital, at which time an aneurysm of the carotid artery had been found and nylon mesh placed around it. Approximately one year before admission the mass recurred.

On admission there was a firm, pulsatile mass (4 by 4 cm.) at the angle of the jaw attached to the deep structures. There was a loud "sea gull" type of systolic murmur radiating upward and downward. Pulsations could not be stopped by compressing the carotid artery.

An arteriogram was performed: "The internal carotid artery and its branches are well outlined and not remarkable. The external carotid is visualized for a short distance of five millimeters. There is an irregular accumulation of the opaque material over an area measuring about 2 × 3.5 cm. in the soft tissue slightly below the angle of the jaw. This is not characteristic and may represent an accumulation of opaque material in an aneurysmal formation in relation to the external carotid artery."

Operation was difficult because of the previous wrapping with nylon mesh. At the bifurcation there was a mass the size of an olive which appeared pulsatile, firm, discrete and rubbery. The mass was dissected free, requiring sacrifice of the external carotid artery.

SUMMARY

Carotid bodies belong to an organ system of mesenchymal or neural origin intimately connected with blood vessels in various parts of the body, and function as chemoreceptors. Tumors derived from them are slow growing and spread essentially by expansion and incorporation of local structures; however, lymph and blood vessel spread does occur. Excision of carotid body tumors should be done without sacrificing the carotid bifurcation since this procedure has a high mortality and disability rate.

Allied tumors arise in other locations, giving rise to characteristic signs and symptoms which demand surgical treatment: the jugular, aortic, ciliary and vagal bodies, and the questionable alveolar, femoral and retroperitoneal bodies.

Eight carotid body tumors and one aortic body tumor have been seen at the Boston City Hospital. One tumor was operated upon in 1887 and may have been the first such tumor resected without sacrificing the carotid bifurcation.

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DISCUSSION

Everett E. O'Neil (Boston, Mass.): I am a little bit confused. I do not know the origin of that "sea gull" murmur. I am not so sure—because I was quite bewildered at the time of this operation which Dr. Byrne described—but that it comes under the heading of a little bit of a bird anyway. I know that he had a great many onlookers from whom I sought solace as well as information, and I am sure I got the "sea gull" murmur from them.

One thing which I think should be emphasized in these tumors which might lead, from what Dr. Byrne has said, to a little confusion on the part of some people is a point that Dr. Frank Lahey made a few years ago. I believe he reported something like fourteen of these tumors which came through the clinic back in 1950. He, with all respect to his technical ability, had a wholesome respect for resection of the carotid body tumors. He took the position that if you were having difficulty with a large carotid body tumor and you were going to compromise the circulation of the brain by damage to the internal or common carotid artery, you had better back out and possibly come back again some other day, or possibly submit these patients to high voltage x-ray.

Lahey took the position that incidence of malignancy in these cases of carotid body tumors is very, very low, and that if the material of the biopsy that you made was negative for malignancy, you were well within the bounds of safety in submitting these patients to x-ray. I am sure that these tumors are not so easy to resect as one would be led to believe.

I would think that since it is a relatively easy anatomical area in which to work once you have the body exposed, one might put in an arterial or vein graft.

Tumors of the Thyroid

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THE thyroid gland is a bilaterally symmetrical organ of internal secretion formed of two lobes, one lying on each side of the trachea, usually below the larynx and commonly united by a thin layer of tissue, the isthmus. Often a third lobe (pyramidal lobe) is present, which arises from the upper border of the isthmus and may extend to the height of the hyoid bone. Inasmuch as the median thyroid component arises as an unpaired outgrowth of the ventral pharyngeal wall and passes down the middle of the neck along the thyroglossal tract, it is not surprising that tumors of the thyroid may be distributed anywhere from the hyoid bone to the thyroid itself. We have never seen tumors of the thyroid above the hyoid bone and in the region of the foramen cecum, although so-called "lingual thyroids" are reported as having adenomatous characteristics [*14*].

The lateral thyroid components arise as paired primordia in the endoderm of the fourth pharyngeal pouch. In former years much was written about the so-called "lateral thyroid carcinoma," but it is now generally accepted that when cancer of the thyroid is found in the lateral part of the neck it is metastatic from a primary focus in the thyroid gland itself.

In a review of the literature the author and co-workers [*14*] found very few cases of residual lateral thyroid components in the neck of patients who had lingual thyroid (eight cases of thirty-six cervical explorations in patients with lingual thyroid). It would seem to us that clinically at least the median thyroid component is the most important; and when it remains at the foramen cecum, very seldom do the lateral thyroid components develop or descend in the neck sufficiently to be recognized at operation.

In any discussion of tumors of the thyroid, consideration must be given to the lymphatic drainage and the venous flow from the organ. The lymphatic channels begin as a rich, delicate network around the thyroid follicles and extend peripherally through the gland into the collecting trunks which drain into various groups of lymph nodes. The medial superior trunks drain upward to the subdigastric, and the intercricothyroid nodes and the median inferior trunks drain into the lower pretracheal and inferior jugular nodes with a few emptying into the brachiocephalic nodes and thymus. The posterior inferior trunks drain into the nodes in the sulcus posterior to the gland along the recurrent laryngeal nerve, and the posterior superior trunks empty into the retropharyngeal nodes. The lateral trunks extend into the internal jugular chain or posterior triangle of the neck, due to the lateral extension of lymphatics beneath the sternocleidomastoid muscle.

The venous drainage is for the most part into the internal jugular veins via the superior and median veins. The inferior veins flow directly into the innominate vein. It is essential, therefore, that any extensive dissection for cancer of the thyroid requires ligation of the veins before attacking the main organ in order to prevent if possible (or at least limit) dissemination of malignant cells through the veins.

CONDITIONS RESEMBLING TUMORS

Cysts of the thyroglossal duct usually offer no problem in differential diagnosis unless they are located low in the neck in the region of the isthmus. Occasionally benign adenomas of thyroid tissue are found as high as the hyoid bone. These are usually firm and globular. Most cysts of the thyroglossal duct sooner or later break down forming a sinus—a condition which is easy to differentiate from tumors of the thyroid.

The *adenomatous* or *multiple colloid goiter* is usually multilocular, although when single it is easily confused with a true adenoma. Although these are most common in endemic

areas where it is presumed that the iodine intake in food and drinking water is deficient, they may occur in non-endemic areas. The pathological specimen shows numerous globules, glossy and translucent in appearance, filled with gelatinous material. They may be located in one section of the gland or may be diffusely distributed throughout. The treatment is surgical excision, either for cosmetic reasons, symptoms due to pressure on adjacent structures or hyperthyroidism. The frequency of carcinoma developing in these goiters is very low, as will be mentioned later in the text.

Various forms of *thyroiditis* sometimes offer a problem in diagnosis, particularly in the subacute or chronic variety. Acute thyroiditis which is uncommon is associated with symptoms of acute inflammation and offers very little difficulty in differential diagnosis. Thyroiditis is usually characterized by a rapid symmetrical or asymmetrical enlargement, firmness of the gland and some fixation to adjacent structures. I have observed that many cases of thyroiditis, such as struma lymphomatosum (Hashimoto) may have a symptom of intermittent hoarseness. This is sometimes helpful in distinguishing between struma and cancer. If hoarseness is due to cancer, it is usually due to permanent destruction of the recurrent laryngeal nerve. Our usual form of treatment of thyroid struma is excision of an adequate amount of gland to reduce the size of the tumor followed by x-ray therapy. Should hypothyroidism develop, it is treated by desiccated thyroid.

BENIGN TUMORS

The vast majority of benign tumors of the thyroid arise from glandular epithelium and are designated as "adenoma." As in previous publications [*15,16*], we followed the classification as suggested by Warren [*17*].

Follicular Adenoma. This tumor has a tendency to form follicles. It is frequently solitary, round or oval, rubbery firm, and has a well developed capsule. It may be located in any portion of the thyroid gland and usually does not attain a very large size. The amount of colloid present causes a variation in the gross appearance. The surface is brown and somewhat translucent. Retrogressive changes may be present due to interference with the blood supply as the tumors enlarge, resulting in softening, cyst formation and hemorrhage.

Follicular adenomas may have a predominant picture of embryonal, fetal, simple, colloid and Hürthle cell. Embryonal adenomas are the most poorly differentiated, with columns of small, closely packed thyroid cells. Fetal adenomas are slightly more differentiated and show miniature follicle formation. Warren [*17*] states that cyst formation and hemorrhage are most common in this type. Simple adenomas show a more well differentiated thyroid tissue with follicles and some colloid contents resembling a normal gland. Colloid adenomas contain an excessive amount of colloid with greatly distended follicles. Hürthle cell adenomas are made up of large acidophilic, granular, epithelial cells known as Hürthle cells. This tumor does not show as much follicular development as some of the others and contains little or no colloid.

From a clinical point of view, it hardly seems necessary to differentiate the simple adenomas into the subgroups, although it is considered by some that the adenomas with less colloid are more apt to have a "precancerous" significance.

Follicular adenomas may occur at any age and are most common in middle life. They are several times more frequent in females than in males. They may remain stationary in size and be symptomless. They may increase slowly, producing pressure symptoms and causing some disfigurement. They may become hyperfunctioning, taking up radioiodine, but only 1 per cent produce clinical hyperthyroidism. Various changes occur, with sudden and alarming increases in the size of the tumor due to hemorrhage.

Clinical differentiation from adenomatous goiter may be made presumptively on the fact that the true adenoma is usually solitary and the remainder of the gland is normal. Should the adenoma arise in a gland already nodular, the differentiation cannot be made with certainty. Differentiation from papillary adenoma, early carcinoma or adenocarcinoma is often impossible on a clinical basis. The hardness of the tumor and increase in growth are presumptive evidence of malignancy.

There are several reasons for the removal of the benign adenoma. The tumor may become large and unsightly or may produce pressure symptoms on adjacent structures in the neck. The most serious problem, however, is the relationship to carcinoma. It is still unknown

whether many adenomas become cancerous or whether they were for years slow-growing cancers and assumed to be adenomas. Cole et al. [4] reported that the incidence of carcinoma in solitary nodules is 24 per cent and in the nodular goiter 11 per cent. Crile and Dempsey [5] reported 10.9 per cent cancer in non-toxic nodular goiters and 24.5 per cent cancer in non-toxic solitary tumors surgically removed.

Reinhoff [12] studied his own personal series of 2,489 patients with thyroid disease upon whom he had operated. Eighty-seven patients (3.4 per cent) proved to have malignant disease. One thousand twenty-nine patients of the total of 2,489 had nodular goiters, of which eighty-seven or 8.5 per cent proved to be carcinoma, and 686 of the 1,029 were solitary nodules in which 17 per cent were malignant. Of the eighty-seven cases of malignant disease, thirty could not be traced; however, information was obtained on fifty-seven in which thirty-two (56.2 per cent) were living and twenty-five (43.8 per cent) were dead. Of those who died in the one- to four-year postoperative group, the malignant growth had spread outside the original nodule. Malignancy was clinically suspected in each of these patients preoperatively. Of the 56.2 per cent of patients who survived for five or more years, all were thought to have clinically benign nodules preoperatively. The malignancy in this group was found to be within the confines of the nodule. Reinhoff goes on to state: "It would therefore seem reasonable to assume that if solitary nodules are removed from the thyroid gland by surgical excision while they are yet clinically benign, even though a pathological diagnosis of malignant change confined to the nodule is reported, the patient has an excellent chance of permanent cure. Conversely, if the malignant change has spread beyond the confines of the nodule, the prognosis is markedly worsened."

We hold that surgical excision of an adenoma, together with an adequate margin of normal adjacent thyroid tissue, is the method of treatment. It should be emphasized that the time of therapy is as soon as possible after the discovery of the disease. Many times what appeared to be a solitary nodule may turn out to be a cluster of colloid adenomas, but the danger of the solitary palpable lump is greater than the risk of the operative procedure. Thyroid operations now are done with so little risk that one cannot consider that seriously in the light of the danger of malignant change.

Papillary Adenomas. This benign epithelial neoplasm is characterized by the production of papillae and a tendency to cyst formation with the papillae growing in the cyst. These tumors are similar to the follicular adenoma in gross appearance except that they are usually cystic, with the adenoma in the cyst. The encapsulation is less marked, as is also the demarcation from the adjacent normal gland. As a rule they are softer than the follicular adenomas.

Microscopically, the cells are cuboidal or columnar, often resembling resting thyroid epithelium. There is not much evidence of cellular activity such as mitosis and nuclear pleomorphism. The connective tissue stalks of the papillae are covered by a thin layer of epithelium. Follicles may be present and may contain colloid. Warren and Meissner [19] emphasize the commonly observed fact that benign papillary tumors are comparatively rare, whereas malignant papillary tumors are the most common thyroid cancer. They state: "A papillary tumor is more likely to be malignant than benign at the time of removal."

The differential diagnosis is essentially the same as for follicular adenoma, and the only real criterion of diagnosis is microscopic examination.

Treatment is surgical removal. The great interest in the treatment of thyroid tumors today is focused upon these papillomas. Since a high percentage become malignant, the discussion is whether they should be removed radically or conservatively. On the whole, these tumors are relatively slow growing and metastasize by way of the blood stream and lymphatics.

MALIGNANT TUMORS

The basis for pathological diagnosis of cancer of the thyroid is the same as for malignant change in other parts of the body. In addition, since many thyroid cancers are slow growing, even after metastasis has occurred, diagnosis often must be based on the invasive characteristic in the local area and their metastases rather than on morphology alone. It is generally accepted that all tumors showing the usually accepted pathological criteria of cancer must be called malignant, whether they grow rapidly or slowly. We believe that one should look upon any tumor as cancer that is invasive

or will metastasize, and they should be treated accordingly. It is obvious that an early radical procedure will prevent or reduce the number of patients who die from cancer no matter what the morphology and natural history of the disease really is.

TABLE I
AGE INCIDENCE IN 112 CASES OF CARCINOMA OF THE THYROID GLAND*

Age (yr.)	No. Cases
1–10	3 (youngest age 4)
11–20	2
21–30	17
31–40	20
41–50	22
51–60	26
61–70	20
71–80	2 (oldest age 80)

* (From: WARD, G. E. and HENDRICK, J. W. Tumors of the Head and Neck. Baltimore, 1950. Williams & Wilkins Co.)

In our series of 112 carcinomas of the thyroid gland studied at the Johns Hopkins Hospital, it was found that seventy-four patients were females and thirty-eight were males [*15*]. This ratio is in contradistinction to that usually encountered in patients with goiter; in the latter the ratio of females to males is about 6:1.

Cancer of the thyroid may occur at any age. (Table 1.) Three patients were under ten years of age and five were under twenty. Winship and Chase [*20*] reviewed 138 reported cases of cancer of the thyroid in children and added 147 unpublished cases located by surveys conducted in the United States, Canada and Western Europe. After their study of these 285 cases of cancer of the thyroid in childhood, they concluded that there was no " . . . remarkable difference in the clinical manifestations, the histologic types, or the progress of the disease" as compared with thyroid cancer in adults.

Samuel Asper, who is in charge of the thyroid clinic at Johns Hopkins Hospital, and his associate, Hunter Wilson, are studying thirty-seven patients under twenty-five years of age who have cancer of the thyroid [*1*]. In eighteen patients the age of onset was under fifteen years. Twelve of these had had previous x-ray therapy about the head, neck or upper chest. One patient received radium therapy for a hemangioma at the sternoclavicular joint. In nineteen patients the age of onset of the cancer was between fifteen and twenty-five years. Two of this group had had previous x-ray therapy.

There are numerous classifications of thyroid disease [*9,10,17*]. In a recent study of patients with cancer of the thyroid seen at the John Hopkins Hospital, Jude, Zimmerman and I used the following three headings: (1) papillary carcinoma, (2) follicular carcinoma and (3) undifferentiated carcinoma including small cell, giant cell and Hürthle cell varieties. Since malignancy in the thyroid usually arises from glandular epithelium, those that are derived from the stroma and lymphatic elements are quite rare.

The majority of students of cancer of the thyroid will admit that a pre-existing nodule is present in the vast majority of patients. In our 112 cases, ninety-seven patients gave a history of abnormality existing prior to the diagnosis of cancer: discrete adenomas in normal position, twenty-three; aberrant position, twenty; multiple adenomas, sixteen; bilateral adenomas, five; diffuse involvement of the entire thyroid, twenty-three; one lobe diffusely involved, ten.

Follicular Carcinoma. These tumors are sometimes called "malignant adenomas." Grossly they appear as a benign follicular adenoma, but under the microscope they show evidence of invasion of blood vessels, of lymph or of the tumor capsule. Invasion of the blood vessels as a criterion of malignancy was first emphasized by Graham [*9*]. Warren [*18*] and others have continued to stress invasion of blood and lymph vessels as a criterion of malignancy, although the adenoma itself might otherwise appear histologically as essentially benign.

Most of these nodules are removed with the clinical diagnosis of a solitary nodule and it is only following microscopic study that the true malignant nature is noted.

The outlook for cure in these cases varies from 80 to 99 per cent. In our study at Johns Hopkins Hospital our five-year salvage was 82 per cent and the ten-year salvage was 60 per cent. (Table 11.) So far as the local growth is concerned, the prognosis is good if removed early and adequately. In thirty-four cases of follicular adenoma with invasion of

TABLE II

CARCINOMA OF THYROID—JOHNS HOPKINS HOSPITAL

End Results	No. Cases Followed up Five Years	Five-year Survival (%)	No. Cases Followed up Ten Years	Ten-year Survival (%)	No. Cases Followed up Fifteen Years	Fifteen-year Survival (%)
Papillary	41	85.3	22	72.2	12	66.6
Follicular	17	82.3	10	60.0	1	0
Undifferentiated	10	50.0	7	28.0	3	0
Small cell	2	0	1	0	..	....
Giant cell	5	40.0	..	.....	*	....
Hürthle cell	3	100.0	1	100.0	..	....

* All patients with giant cell carcinoma died before 6 yr., except one who lived 10.6 yr.

blood vessels studied by Warren [*18*], metastases developed in only two.

The treatment as recommended in the literature varies from excision of the tumor with its capsule and a good margin of adjacent thyroid tissue, to excision of the entire lobe, and excision of the entire lobe with radical neck dissection. In the case of follicular adenocarcinoma, which is a more malignant stage of the same tumor, the more radical procedure is adhered to. In our series we have put all these in one group of follicular carcinoma. It has been my personal practice to carry out a radical neck dissection in cases diagnosed definitely as cancer, whether they be follicular or papillary. This practice has been based on the fact that any tumor, no matter how small, may have metastasized to lymph nodes; and if one can excise the entire lymph-bearing area of the neck, a higher percentage of cancer will be eradicated. So far we have not had a large enough series done over a long enough period of time to furnish statistics to substantiate our stand.

With the more malignant types of follicular carcinoma, metastases to bone and lung are quite common although they may not become evident for a considerable period of time.

Papillary Carcinoma. This group also may be subdivided into the less malignant type of papillary adenoma which grossly looks benign but microscopically shows evidence of invasion of either blood or lymph vessels or the tumor capsule, and the somewhat more malignant group of papillary adenocarcinoma which is occasionally called "papillary cystadenoma." The gross appearance is identical with the benign papilloma, but the differential diagnosis is made on microscopic examination. In these tumors there is more likely to be lymphatic than blood vessel invasion. Capsular invasion is also common. Since many papillary tumors have been present for a considerable time (some benign and others malignant), the question naturally posed is, How many of these tumors are malignant from the very beginning? For this reason, every solitary nodule should be removed and submitted to careful microscopic study. Early invasion of the lymphatics means early metastasis to the regional lymph nodes. It is my personal practice to perform a radical neck dissection in the hope that one can remove all the metastatic disease in the neck as early as the diagnosis is made. In our recent series the five-year salvage of papillary carcinoma was 85.3 per cent, and the ten-year salvage 72.2 per cent. Since radical operations have been performed over a shorter period than the previously used wide local excision and repeated treatment of the lymph nodes, one cannot give a comparison of the five-year result in the two methods of treatment.

Because of the greater tendency of lymphatic invasion, the prognosis is more guarded than in the lower grade follicular carcinomas [*19*]. This view of prognosis seems a bit at variance with our statistics which show that the five- to ten-year salvage is better in the papillary than the follicular carcinomas.

In the papillary carcinomas, focal areas of calcification are seen. Papillary carcinomas are the most common of all thyroid malignancies and are the most frequent type of thyroid cancer in young people. They also occur more often in females than in males. Cervical lymph node metastasis often is the first symp-

tom noted by the patient; hence, the name "lateral aberrant thyroid" tumor. Careful studies by many authors have shown that even though a primary site cannot be felt in the thyroid, close observation of the operative specimen will reveal the presence of a focus of

TABLE III
DISSECTIONS FOR PAPILLARY CARCINOMA (1946–1953)*

	Metastases to Nodes		
	Clinically Negative	Clinically Positive	Clinically Doubtful
Neck dissections with metastasis to node.	67	104	11
Proved pathologically	41 (61.2%)	...	113 (96%)

* (From: FRAZELL, E. L. and FOOTE, F. W., JR. *Cancer*, 8: 1164–1166, 1955 [8]).

papillary cancer in the thyroid from which the metastasis has occurred into the lymph nodes of the neck.

Frazell and Foote [8] found the following interesting facts about papillary thyroid cancer: At the Memorial Hospital in New York from 1946 through 1953, 182 specimens of radical neck dissections for papillary cancer of the thyroid were taken from 164 patients. Eighteen patients underwent bilateral neck dissection. The over-all lymph node involvement was 84.6 per cent. If the neck was clinically positive or suspicious, the microscopic examination revealed involvement of 96 per cent. (Table III.) When the neck was clinically negative, positive nodes were found in 61.2 per cent. The conclusions of Frazell and Foote are that a radical neck dissection should be performed when and as soon as diagnosis of papillary carcinoma of the thyroid is made.

Colcock [3] reports from the Lahey Clinic as follows: "We believe that all solitary nodules of the thyroid regardless of their size and regardless of the age of the patient should be removed whenever they are discovered." His practice is to remove the nodule with an ample margin of apparently normal thyroid tissue. Frozen section is made; and if the diagnosis is positive for cancer, radical neck dissection is performed immediately. If there is any question of the diagnosis, the surgeon waits for a permanent section to be absolutely sure of the diagnosis. He states that indication for surgery in patients with multinodular goiter is the same as for "solitary nodule," but the relative importance of these indications vary considerably depending on which type of goiter is present. He holds that carcinoma in multinodular goiter is less than in the solitary nodule, but secondary hyperthyroidism is more frequent in multinodular goiters, particularly in the older age group.

On the other hand, Crile [6] lists fourteen reasons for not performing radical neck dissection for papillary cancer of the thyroid:

1. There are no reported large and long-term follow-ups of cases with radical operation which show as good a result as the conservative method.

2. Anatomically there is no continuity of tissue planes between the thyroid and the lateral neck tissue. *Comment:* Neck dissection in continuity with the thyroid can be performed if the operator is careful to dissect from the posterior part of the neck forward.

3. There is no such thing as block dissection for carcinoma of the thyroid. *Comment:* With this I do not agree.

4. All carcinoma of the thyroid with exception of rare upper pole carcinoma metastasize along the central area into the mediastinum. *Comment:* This may be true, but following this argument into other areas, the surgeon would not perform radical resections of adjacent lymph nodes in treating carcinoma of the oral cavity and breast. He hopes to be able to get around the metastases while they are limited.

5. Only once in 100 cases was the sternocleidomastoid muscle involved. That was in a woman who had had carcinoma thirty-seven years. *Comment:* Evidently, the argument is based on the assumption that a radical neck dissection is multilating. With this I disagree. There may be some scarring and flattening of one side of the neck, but in our cases most women have not objected to this moderate amount of disfigurement in view of the removal of the diseased areas.

6. Sternocleidomastoid muscle is of great cosmetic value in women. *Comment:* This is answered under No. 5.

7. Sacrifice of the eleventh nerve is painful and disabling. *Comment:* To this I will agree, but in many patients with early cancer the eleventh nerve may be saved by dissecting

through the sternocleidomastoid muscle on the lateral side and away from the areas of lymph node drainage. If this seems unwise, the sacrifice of the eleventh nerve is one of the prices to be paid for a more adequate cancer operation.

8. Adequate node dissection can be obtained without loss of important nerves and muscles.

9. The natural history of zones of metastases differs from cancer of the mouth and these cannot be compared with each other. He holds that cancer of the thyroid metastasizes by virtue of emboli like cancer of the lip. *Comment:* This is a rather weak argument.

10. Papillary carcinoma regresses with treatment by desiccated thyroid glands. Crile uses 3 gr. daily on the theory that the desiccated thyroid suppresses thyroid-stimulating hormone of the pituitary. *Comment:* Before one would accept this statement, a much larger series followed up over a long period of time is needed.

11. Under four years of age, the tumor shows a mixture of follicular and papillary carcinoma, with the follicular carcinoma giving as good a result as papillary. *Comment:* This is no argument against radical neck dissection.

12. Of 107 patients with papillary carcinoma operated upon by Crile, 75 per cent had metastases at the time of operation; 20 per cent required a second operation. *Comment:* This in itself indicates that the first operation was inadequate.

13. Crile stated that none of the patients with papillary carcinoma died of cancer, even though some were followed up fifteen or eighteen years. *Comment:* Other authorities report death from papillary carcinoma. Braund [2], in reviewing his cases of papillary carcinoma of the thyroid, found that over twenty patients had died of the disease.

14. He offers his records and slides for anybody to study. For some unknown reason he states that the burden of proof is on the surgeon who advises mutilating operations. *Comment:* Again I say, radical neck dissection is not multilating if it is performed correctly.

In our aforementioned incomplete study of patients with carcinoma of the thyroid operated upon at the Johns Hopkins Hospital we were able to trace seventy-eight. (Table II.) Of forty-one cases of papillary carcinoma, 85.3 per cent of the patients survived five years, 72.2 per cent survived ten years and 66.6 per cent were alive and well fifteen years after operation. Of seventeen cases of follicular carcinoma, 82.3 per cent of the patients lived five years, 60 per cent lived ten years free of disease and none survived fifteen years. Of the ten cases of undifferentiated cancers, 50 per cent of the patients lived five years, 28 per cent lived ten years and none survived fifteen years.

TABLE IV
CARCINOMA OF THYROID—JOHNS HOPKINS HOSPITAL
ANALYSIS OF TREATMENT

	Total No. Cases	Single Operation	Multiple Operations	Postoperative X-ray Therapy
Papillary	70	37	33	30
Follicular	37	23	14	11
Undifferentiated	16	12	4	9

Our study is incomplete, but Table IV gives some idea of the number of patients treated by one or two operations and those receiving postoperative roentgen therapy. Postoperative x-ray therapy is of value in treating follicular and papillary carcinomas when given over the neck and some distant metastases. The small cell and giant cell tumors are not radiosensitive. Horn and Dull [11] report on the five- and twelve-year survivals of patients with cancer of the thyroid treated at the University of Pennsylvania (1933–1947), as shown in Table V in which we have converted their classification into ours.

Undifferentiated Carcinoma (carcinoma simplex). *Small cell carcinoma* is an anaplastic carcinoma made up of small cells, extending diffusely in all directions. As the name "undifferentiated" implies, there is little follicle or colloid formation. These tumors are malignant and invasive, extending widely throughout the thyroid gland itself and into surrounding structures, including the isthmus and the opposite lobe. When the neck is opened, the tumor often appears diffuse throughout the thyroid as a firm, white, ill defined mass.

There is no differentiation of these tumors into the follicular or papillary variety. Histologically, the tumor is seen to be composed of small, closely packed cells growing in strands or clusters. In other types there is more diffuse extension and frequently the tumor is difficult

TABLE V

FIVE- AND TWELVE-YEAR SURVIVALS OF PATIENTS WITH CARCINOMA OF THYROID
(HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA, 1933–1947)

	No. Patients Treated More Than Five Years Ago	Five-year Survivals		No. Patients Treated More Than Twelve Years Ago	Twelve-year Survivals	
		No.	%		No.	%
Malignant adenoma	16	9	56	8	2	25
Papillary, follicular or mixed	54	40	74	16	6*	38
Adenocarcinoma	26	14	54	12	4	33
Undifferentiated	16	3	19	8	1	12.5
Totals	112	66	59	44	13	30

* Three patients with papillary carcinoma are living with the disease.

to differentiate from lymphoma, particularly lymphosarcoma. Mitoses are numerous.

There is a frequent history of a pre-existing mass in the thyroid for years, which is another important fact pointing toward the need of early removal of thyroid nodules.

The prognosis is poor since by the time the patient comes to surgery the local growth is so extensive as to prevent adequate removal. Radiation therapy is palliative. The five-year survival is given between 20 and 30 per cent. In our series the number was too small for statistical review.

Treatment is radical surgery if possible. Radioiodine is of no value.

Giant cell carcinoma is a highly malignant, undifferentiated cancer with the characteristic of having large giant cells on histologic examination. Grossly, this tumor appears similar to the small cell carcinoma but may be more bulky in size. Microscopically, pleomorphism is commonly noted. Mitoses are frequent. Many multinucleated giant cells are intermixed with various forms of small spindle cells.

This tumor is uncommon in patients under the age of sixty. Here, again, often there is a history of a pre-existing mass which suddenly began to grow. These tumors grow rapidly and are extensive by the time they reach the surgeon.

The prognosis is extremely poor. It is interesting that one of our five patients lived sixteen years. Frazell and Foote [*8*] found that the average duration of life from the diagnosis to death was 4.8 months in thirty-eight cases studied.

Hürthle cell carcinomas arise from Hürthle cells which many authorities believe are merely altered thyroid epithelial cells. We have put them separately in our chart but prefer not to differentiate them on a clinical basis.

Miscellaneous Malignant Tumors. Rarely an *epidermoid carcinoma* arises in the thyroid. Nests of squamous epithelium are occasionally found in the normal thyroid which may represent a persistence of vestigial structures or embryonic rests. Epidermoid carcinomas usually are highly malignant.

Other malignant tumors that occasionally occur in the thyroid are *fibrosarcomas, lymphomas* and, rarely, *metastatic tumors* from other parts of the body.

RADIOIODINE (I^{131}) THERAPY OF CANCER OF THE THYROID

When radioiodine was first used in the treatment of carcinoma of the thyroid, hopes were high for great beneficial results because the normal thyroid concentrates iodine. It was soon found that only those cancers will be affected which are sufficiently well differentiated to concentrate iodine (more commonly alveolar and follicular types and to a lesser amount papillary, solid and Hürthle cell varieties) [*7*]. It has also been shown that cancers concentrating little or no iodine may be stimulated to pick up iodine by ablating the normal thyroid gland with radioiodine or surgically removing the entire gland.

A technic practiced by some surgeons [*13*] is to use thyrograms before surgery to determine whether a thyroid nodule will take up iodine.

A filling defect may suggest carcinoma, but other possible causes of the lack of uptake in a given area are fibrosis, cystic degeneration or a non-functioning adenoma. Normal thyroid tissue takes up iodine. Tumor tissue may take it up poorly or better than normal tissue.

Screening of the entire body after a test dose of I^{131} may indicate metastases.

When the entire gland has been removed surgically or ablated by radioiodine, metastases may be encouraged to take up I^{131} by the administration of thyrotropic hormone.

It is a good practice to remove all the canecr that can be resected. This means a block dissection of the neck nodes and at least the involved thyroid lobe and isthmus—many times the entire gland. When the entire gland has been excised and when metastases appear, a test dose of I^{131} is given to determine the ability of the metastatic deposits to take up the iodine. Uptake may be enhanced by giving thyrotropic hormone (TSH).

When the entire gland has not been removed, it should be ablated by I^{131} or the patient reoperated upon and the remainder of the thyroid excised. Therapeutic doses of I^{131} should be given along with TSH if needed to increase the iodine uptake.

It is unfortunate that many cancers of the thyroid and their metastatic deposits will not concentrate I^{131}. The outlook in such cases is bad.

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DISCUSSION

Everett E. O'Neil (Boston, Mass.): Would anyone like to take up the bat with this? Dr. Dunphy, I did not look in your direction, but I was hoping I could draw you out.

J. Englebert Dunphy (Boston, Mass.): I will be very brief in summarizing my impression of this paper. I have no objection to Dr. Ward performing radical neck dissections for papillary carcinoma of the thyroid, so to speak, on sight. But I do not believe from what I can read—trying to be an objective observer—that to date his results indicate this procedure is something that must be performed by all surgeons. I do not think that the final chapter has been written.

I think that what we need is less emotionalism and more facts, and it will take a little more time to produce this. I wish that I believed, as Dr. Ward does, that all you have to do to cure cancer is to cut it out. Maybe it is because I have bad luck. It seems to me that cancer is a very bizarre disease which produces fatalities so often by other than just metastases to the lymph nodes.

Let us take his figures in the intermediate and low grade malignancy. Let us say, roughly, 20 per cent of patients die or do not survive five years. Dr. Crile's figures are in about the same rate—20

to 25 per cent. Now in that group, some of those are due to blood-borne metastases, which cannot be cured by radical neck dissection.

Therefore, to me, it would take an awful lot of study really to clear the problem of where dissection begins and ends for papillary tumors. I just wish I was as sure as either Dr. Crile or Dr. Ward. I am just not convinced that we know the answer.

DR. O'NEIL: I wish, Dr. Ward, that you would in a word or two explain to this group what you mean by radical neck dissection following the removal of a solitary malignant nodule.

DR. WARD: I think Dr. Dunphy and I are not so far apart. I tried to say that Dr. Crile must have a larger series of cases before he proves his point, and I must also. I should say "we" must prove our point, those of us who believe in the radical procedure.

I might go back and make a more philosophical statement to underline the remarks, namely, that surgery and radiation therapy are not the answer to cancer anyhow. However, my contention is that if you know a patient has cancer of the thyroid, whether it be papillary or some other type, you should make an honest effort to resect it. I think that is the best method of treatment today and until somebody has proved otherwise.

I think it is dangerous to put out to the general public that papillary cancer does not have to be operated upon. So far there are not sufficient data to support this statement and many people will not be operated on after reading such a statement who otherwise might have had their lives prolonged for an indefinite period. Just as is done in other investigations, the patients with extensive disease should be used as trials instead of any and all comers. We should carry out the best treatment known to date in the early cases and experiment with those whose disease has been resistant to the well adopted methods of therapy.

Now, what do I mean by radical neck dissection? When you and I started in surgery, sir, radical neck dissection meant dissection of the anterior triangle. Radical neck dissection now means, to me at least, removal of the lymph nodes from the mastoid down to the clavicle, both anterior and posterior triangles. I do not always take out the submaxillary salivary gland in thyroid cancer; but if there are many suspicious nodes in that area, I do. It means taking out preferably the entire thyroid, so that I can go ahead and use radioiodine later on if necessary. The dissection should extend as far back as the trapezius muscle posteriorly, and include the jugular vein and the sternocleidomastoid muscle on that side.

Some years ago, while experimenting with hematoporphyrins as a means of visualizing lymph nodes at the operating table, it was found that there were lymph nodes much farther back and much farther out from the area of dissection than was anticipated, so it takes a rather radical procedure to remove all the lymph nodes.

DR. O'NEIL: I would believe with Dr. Dunphy that that is radical neck dissection, perhaps, and Dr. Dunphy's reluctance to admit that the average surgeon who met with a solitary adenoma which is malignant should think twice before performing the type of surgery that Dr. Ward has suggested. I am sure that even in Dr. Ward's hands it is a formidable procedure, but what would it be in the hands of a relative neophyte in the field of thyroid surgery?

Tumors of the Parathyroid Glands

PRIMARY HYPERPARATHYROIDISM

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PRIMARY hyperparathyroidism, the condition resulting from hyperfunctioning tumors of the parathyroid glands, is a fairly common, potentially fatal disease which is curable in most cases if treatment is instituted before progressive renal disease develops. Neither diagnosis nor treatment is particularly difficult, although diagnosis is rarely made before complications involving the skeleton or urinary tract have developed. The osseous complication, generalized osteitis fibrosa cystica, is somewhat unusual, whereas complications involving the urinary tract, particularly urinary lithiasis, are common, It has been estimated that probably 5 per cent of all cases of radiopaque urinary lithiasis and possibly 15 per cent of cases of recurrent lithiasis result from hyperparathyroidism.

PATHOLOGIC ASPECTS

In somewhat more than 80 per cent of cases hyperparathyroidism results from a single adenoma, in less than 10 per cent from multiple adenomas, and in about 10 per cent from primary or wasserhelle hyperplasia. Malignant tumors are, fortunately, rather rare, accounting for not more than 1 to 2 per cent of cases.

Adenomas vary in size from tumors as large as a normal parathyroid gland to tumors weighing more than 100 gm. In more than half the cases in the Mayo Clinic series the adenomas weighed less than 1 gm., while adenomas weighing more than 10 gm. were found in less than 10 per cent of cases. Regardless of size, adenomas have a rather characteristic yellow-brown color which permits their recognition grossly. Microscopically, the most striking feature is the virtual absence of stromal fat, which makes up 40 to 60 per cent of the bulk of normal parathyroid tissue. One type of cell may be predominant, but all types of parathyroid cells usually are present. (Fig. 1*a*.)

The usual adenoma is a true solitary tumor. In an occasional case the parathyroid tumor seems to be made up of multiple nodules of different sizes, a change somewhat analogous to multiple nodular goiter. In cases of this type multiple glandular involvement is more common than in the cases of solitary adenomas.

Primary or wasserhelle hyperplasia involves all parathyroid tissue. The four parathyroids may not be enlarged symmetrically, so that grossly, one or even two glands may seem uninvolved. They appear somewhat more chocolate brown than the adenomas. The size and form of the glands vary greatly. The resected hyperplastic tissue in one case in the Clinic series weighed 134 gm. There is no correlation between the intensity of the hyperparathyroidism and the mass of the hyperplastic tissue. The condition is characterized microscopically by uniformly enlarged cells with rather featureless, clear cytoplasm and nuclei oriented toward narrow bands of stromal connective tissue which is not prominent. (Fig. 1*b*.) The microscopic appearance of wasserhelle cell adenomas is quite similar but the cytology is somewhat more varied, and all glands are not involved. (Fig. 2*a*.)

The recognition of parathyroid carcinomas has proved unusually difficult. (Fig. 2*b*.) Mitotic figures, bizarre nuclei and giant cells are found in clinically benign tumors, while other metastatic lesions have a completely benign appearance. It is agreed at present that tumors capable of metastasizing cannot be distinguished histologically from presumably

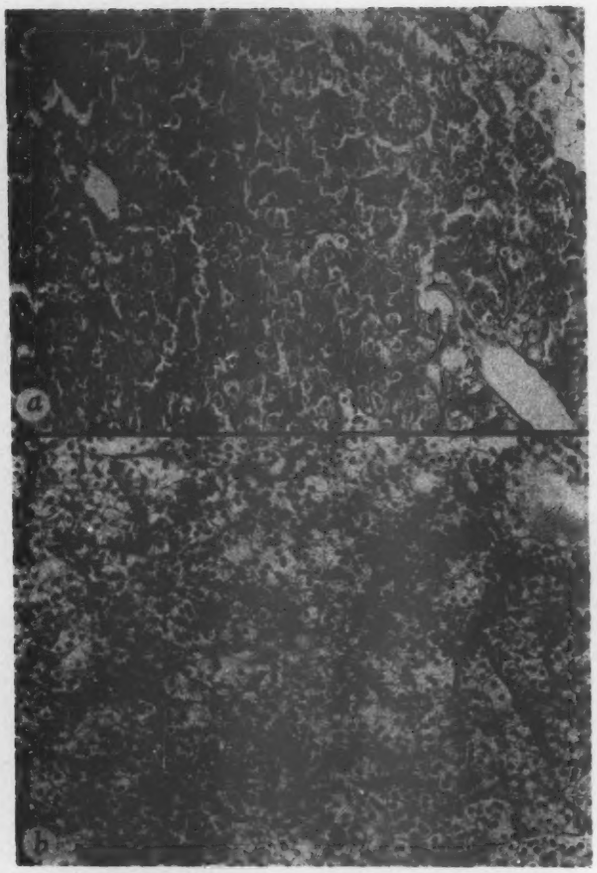

FIG. 1. (*a*) Predominantly oxyphil adenoma. Chief cells and wasserhelle cells in upper right corner. The oxyphil granular cytoplasm is striking in stained sections. Hematoxylin and eosin, original magnification × 150. (*b*) Wasserhelle hyperplasia as it appears in fresh frozen sections. The cells are monotonously similar. Hematoxylin and eosin, original magnification × 150. (From: BLACK, B. M. Hyperparathyroidism. Springfield, Ill., 1953. Charles C Thomas.)

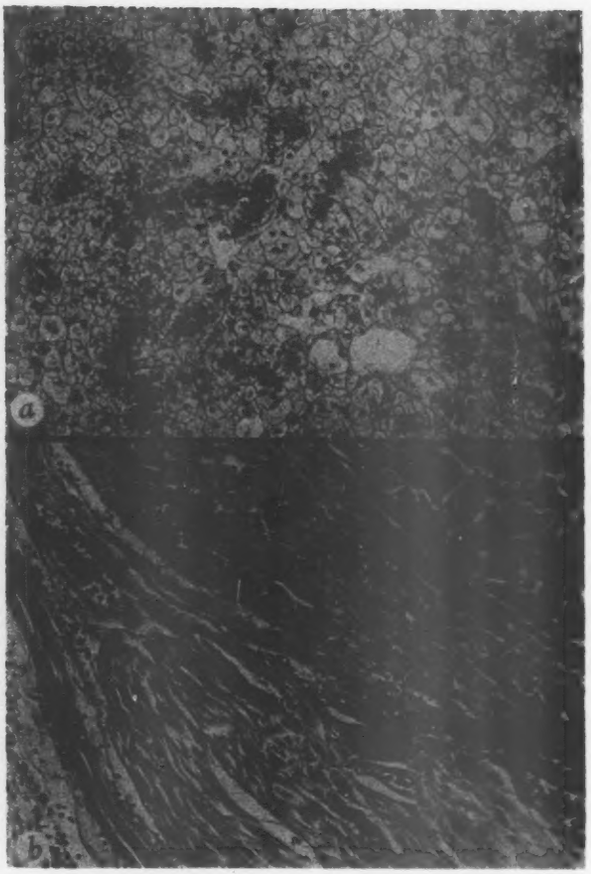

FIG. 2. (*a*) Wasserhelle cell adenoma. The cells are more varied and nuclei less regularly situated than in wasserhelle cell hyperplasia. One parathyroid only was involved. Hematoxylin and eosin, original magnification × 150. (*b*) Parathyroid carcinoma. The lesion recurred locally and lymph nodes and lungs were involved metastatically. Hematoxylin and eosin, original magnification, × 145.

benign adenomas. Benign adenomas, however, are never locally invasive.

Hyperparathyroidism, however, is the same regardless of the lesion of the parathyroids. A crude correlation exists between the size of the adenomas and the intensity of the disease; that is, with marked hypercalcemia the adenomas tend to be large. Osteitis fibrosa cystica is more likely to develop if hyperparathyroidism is severe than if it is minimal, so that, in general, larger adenomas are to be expected in patients with osseous disease.

SYMPTOMS

The fundamental metabolic changes of hyperparathyroidism are increased concentration of calcium and decreased concentration of phosphorus in the serum, and increased excretion of both in the urine. Hypercalciuria presumably accounts for urinary lithiasis and for the deposition of calcium in the renal tubules known as renal calcinosis. The osseous disease results from the continued loss of calcium and probably from the direct effect of the hormone on bone. The clinical importance of the latter is debatable since the development of osseous disease seems to depend entirely on calcium balance. If the intake of calcium is adequate to balance the loss, clinically recognizable osseous disease apparently does not develop.

Hyperparathyroidism obviously must be present before complications develop. The two types of complications may occur singly or together, or they may not have developed,

so that the absence of either skeletal changes or complications involving the urinary tract has no bearing on diagnosis. The clinical findings in 207 consecutive cases are shown in Table 1.

Symptoms of Hypercalcemia. Hypercalcemia *per se* gives rise to symptoms involving the gastrointestinal tract and skeletal musculature. They include lassitude and weakness, loss of appetite, nausea and vomiting, gaseous distention, and constipation. The intensity of the symptoms varies directly with the degree of hypercalcemia. The symptoms are of little value in suggesting the diagnosis since they resemble closely those of purely functional states.

TABLE 1
PRIMARY HYPERPARATHYROIDISM: 1928–1954
CLINICAL FINDINGS (207 CASES)

Complications	Patients	Per cent
Osseous	25	12
Osseous and urinary	35	17 } 82
Urinary	135	65 }
Neither osseous nor urinary:	12	6
Backache	3	...
Polyendocrine adenomas	4	...
Adenoma found during thyroidectomy	2	...
Tumor of mandible	1	...
Adenoma found at necropsy	1	...
Aching of muscles	1	...
Totals	207	100

Symptoms Pertaining to the Urinary Tract. Parathyroid hormone is a potent diuretic and in all cases polyuria and polydipsia are present. Polyuria may be sufficiently marked to suggest diabetes insipidus. The sudden withdrawal of the excess hormone by removal of the tumor causes temporary oliguria or, in severe cases, even temporary anuria.

Urinary lithiasis, as previously stated, is by far the most common complication of hyperparathyroidism. Stones may form at any time during the course of the disease. In some cases many stones form, while in others stones form only occasionally. Recurrent lithiasis is the rule so long as the disease persists, although the diagnosis has been made in many cases after the passage of a single stone. The stones of urinary lithiasis of hyperparathyroidism do not differ in any way from calcium-containing stones of other diseases. Regardless of statements to the contrary, staghorn calculi do form. Unless a urologic cause for recurrent stones (such as stasis and infection) is obvious, the possibility of hyperparathyroidism should be considered strongly.

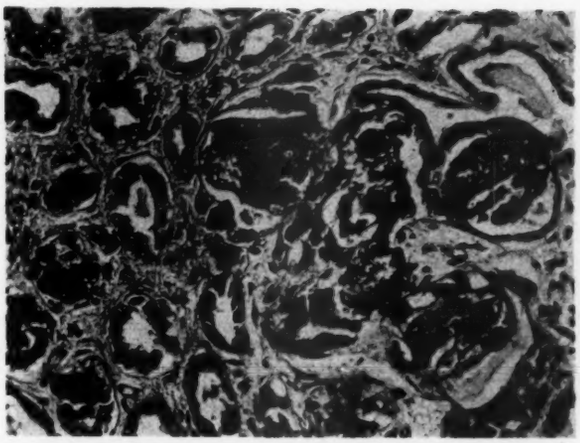

FIG. 3. Section showing evidence of renal calcinosis. Patient died of renal insufficiency. Hematoxylin and eosin, original magnification × 235. (From: BLACK, B. M. Hyperparathyroidism. Springfield, Ill., 1953. Charles C Thomas.)

In addition to stones in the lower portion of the urinary tract, calcium may be precipitated in the kidney. (Fig. 3.) Renal calcinosis, sufficiently marked to be demonstrable roentgenographically, is far less common than lithiasis. It also is far more ominous since it is invariably associated with some impairment of renal function. Impaired renal function often is present in the absence of evident calcinosis.

Symptoms of Osteitis Fibrosa Cystica. The osseous complications of hyperparathyroidism vary from minimal decalcification, which may be asymptomatic, to frank osteitis fibrosa cystica. In keeping with other metabolic diseases of bone, the entire skeleton is involved, although this may not be evident roentgenographically. Localized changes such as cysts, giant cell tumors, gross deformities and fractures may be so prominent that the generalized nature of the process is not recognized. Osteitis fibrosa cystica invariably is associated with an increase in alkaline phosphatase. Unless the alkaline phosphatase is increased, the condition cannot be recognized roentgenographically.

The actual symptoms are extremely varied. The bones may be, and often are, exquisitely tender. Gross deformities usually appear in

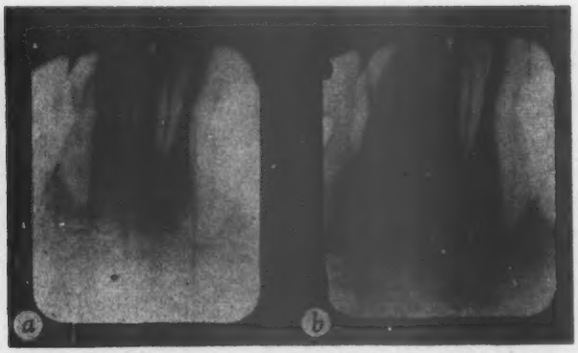

FIG. 4. (*a*) Before development of osteitis fibrosa cystica. (*b*) After development of osteitis fibrosa cystica. The lamina dura has disappeared completely; note marked demineralization of mandible without change in teeth.

time. These include loss of height as a result of collapse of vertebrae, distortion of long bones resulting from bending and fractures, and deformities produced by cysts and osteoblastomas. Giant cell tumors of the jaw may suggest the diagnosis. Fractures of long bones tend to occur through a cyst or tumor. Incidentally, the fractures heal normally except for the complicating factor of the cyst.

FIG. 5. Subcortical decalcification of long bones. Marked demineralization and distortion of internal architecture are evident.

DIAGNOSIS

The diagnosis of hyperparathyroidism should be considered in all cases of renal lithiasis in which the stones contain calcium, in cases of polyuria and polydipsia, and in cases of generalized osseous disease. The roentgenologic changes of osteitis fibrosa cystica are so definite that the diagnosis should present few difficulties. In addition to generalized demineralization, the internal architecture of bone is grossly deranged and cysts and osteoblastomas, which appear as cysts, are common. The ground-glass appearance of the skull and disappearance of the lamina dura have been emphasized for years. Dental roentgenograms are of particular value since the undecalcified teeth provide an excellent index of decalcification of the jaws. (Fig. 4*a* and *b*.) The most pathognomonic change is a rather typical subcortical lace-like decalcification of long bones. (Fig. 5.)

In all other cases the diagnosis must be established by means of laboratory tests. In practice the chief difficulty has to do with the accuracy of determinations of serum calcium. Unless consistently accurate determinations of calcium can be carried out, the diagnosis can be seriously considered in only the most obvious cases.

If renal function is normal, the serum calcium is elevated and the phosphorus is depressed. Hypercalcemia may be minimal indeed. The values for calcium in the Clinic series have varied from 10.1 to more than 18 mg. per 100 cc. of serum. The value for calcium in 14 per cent of cases was less than 11 mg., and in more than 50 per cent of cases it was less than 12 mg. (Fig. 6.) Hypophosphatemia is less striking and less important from the standpoint of diagnosis than is hypercalcemia. Values of less than 3.5 mg. per 100 cc. of serum are found if renal function is normal. Some degree of renal impairment is common, however, and in these cases the value for phosphorus may be normal or even elevated. Some test of renal function, such as the measurement of blood urea, must obviously be carried out in order to evaluate properly the results of the phosphate determination.

At one time studies of calcium balance, such as the Aub test, were employed widely as a diagnostic aid. Unfortunately, from the standpoint of diagnosis, it is now known that the majority of patients with renal lithiasis, and

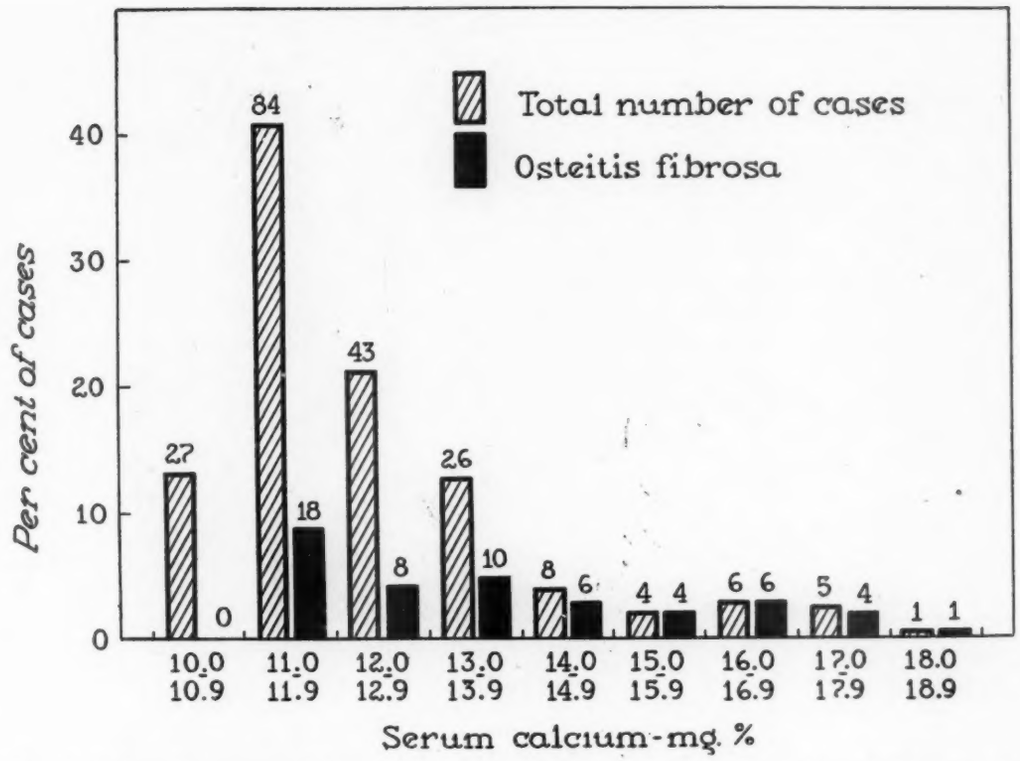

FIG. 6. Values for serum calcium in 207 consecutive cases. With higher calcium levels, osteitis fibrosa cystica is usually present.

practically all patients with recurrent lithiasis, excrete abnormally large amounts of calcium in the urine. Since idiopathic hypercalciuria is far more common than hyperparathyroidism, the finding of hypercalciuria in cases of renal lithiasis is often frankly misleading.

There is some interest at present in devising other tests to discriminate between isoparathyroidism and hyperparathyroidism. Among these may be mentioned tests based on phosphorus deprivation, on phosphorus turnover, on calcium loading and on both calcium and phosphorus loading. So far none has proved clearly superior to determinations of serum calcium in revealing minimal hyperparathyroidism.

Differential Diagnosis. Since the diagnosis is based essentially on the presence of hypercalcemia, other causes of hypercalcemia must be excluded. These include increased blood calcium associated with atrophy of bone owing to disuse, hypervitaminosis D, milk-alkali syndrome, osteolytic metastatic carcinoma, multiple myeloma and sarcoidosis. If hypercalcemia due to other etiologic factors is methodically excluded, the differential diagnosis should not be particularly difficult. Sarcoid was formerly particularly troublesome. It has been learned recently that if hypercalcemia is associated with sarcoid, the value for calcium reverts to normal promptly after cortisone or ACTH is administered.

TREATMENT

The only known treatment of hyperparathyroidism is the removal of the lesion or lesions of the parathyroid glands. The surgical difficulties have to do with the widespread region in which the parathyroids may be located, and with the minute size of many adenomas. Since more than one gland may be involved, it is necessary to identify the four parathyroids routinely. This is the only way, at least, that one can be certain of not missing multiple adenomas. The presence of a pathologist competent to recognize from fresh-frozen sections normal and atrophic parathyroid tissue, parathyroid adenomas and wasserhelle hyperplasia is imperative.

It is most fortunate that the anatomy of the parathyroids is far more constant than was supposed previously. Otherwise treatment would be both uncertain and unsatisfactory. Theo-

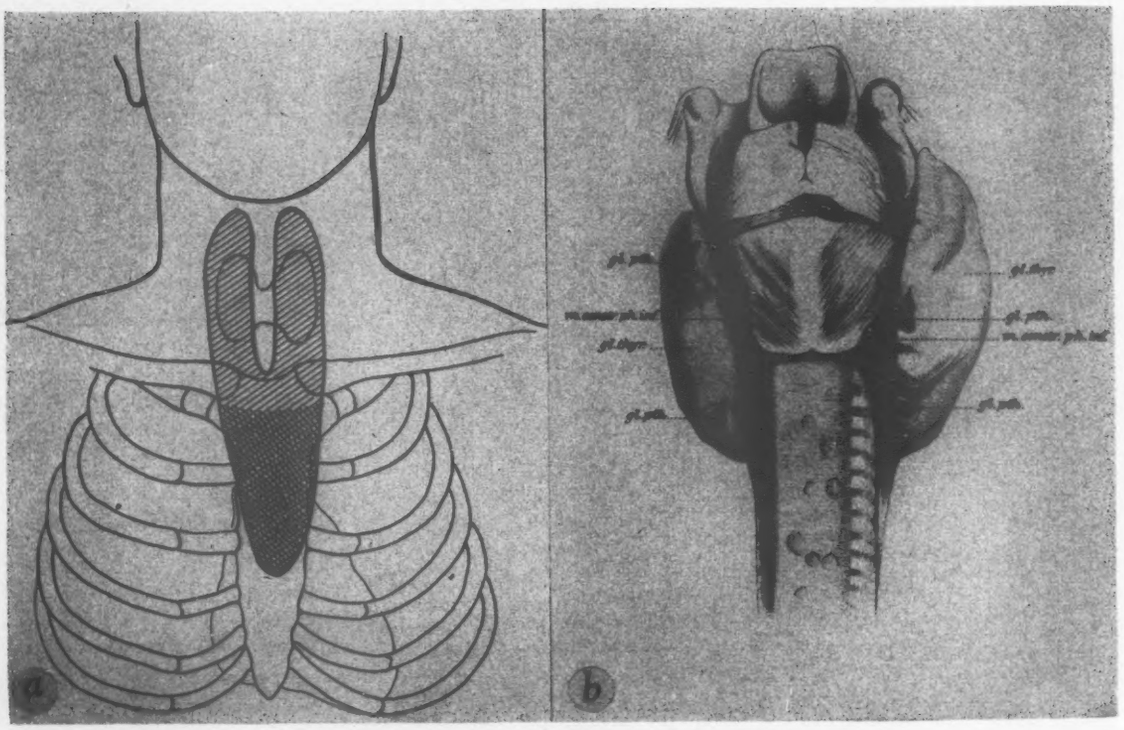

FIG. 7. (*a*) Possible location of parathyroid glands. Glands in the region indicated by deeper shading require mediastinotomy for their exposure. (*b*) Sandström's original illustration (1880) of the four parathyroid glands. The superior glands are usually located more medially than shown. (From: BLACK, B. M. Hyperparathyroidism. Springfield, Ill., 1953. Charles C Thomas.)

retically, the parathyroids may be located anywhere in the visceral compartment of the cervical fascia or anterior-superior mediastinum from the upper border of the larynx above to the pericardium below. (Fig. 7*a*.) In fact, more than 90 per cent of glands are situated in the immediate vicinity of the thyroid or within 3 cm. below the inferior poles, and in the majority of cases the location of the glands is reasonably constant. (Fig. 7*b*.) The superior glands are located so far medially that they are more properly described as lying on the hypopharynx than on the thyroid. The inferior glands are located more laterally and anteriorly. They usually lie anterior to or in the plane of the inferior thyroid veins; if they are below the thyroid, they are associated often with the cervical prolongation of the thymus. Mediastinal parathyroids are usually closely associated with the thymus, and they may be located within the gland.

In addition to variations in location dependent on embryologic descent, enlarged glands or adenomas may be displaced into the mediastinum by the same forces which cause thyroid adenomas to descend into the thorax. Adenomas may be displaced either into the posterior or anterior mediastinum depending on their location before displacement. Enlarged superior glands, originally located dorsally and medially, tend to descend into the posterior-superior mediastinum, while inferior glands descend into the anterior mediastinum. In either case, a vascular pedicle descends from the neck into the thorax, by which the displaced adenoma often can be found and removed.

With experience, a normal parathyroid gland can be recognized grossly with some confidence from its yellow-brown color, delicate capsule and fatty envelope. In some cases, particularly if the gland is atrophic, the color approaches that of fat and gross identification becomes more difficult. The staining of tissues with blood completely obscures the color of the parathyroids and must be avoided most carefully. The dissection must be meticulous and therefore it is usually time consuming.

Cervical Dissection. Cervical dissection, which is always carried out first, is done through the usual incision for thyroidectomy. The lobe of the thyroid is elevated and rotated medially

as far as possible, and the recurrent laryngeal nerve and inferior thyroid artery are exposed. The two parathyroids on the side are then found. If a gland is not present in its usual location, the dissection is extended to include the region in which the gland could theoretically be located. It is not permissible to extend the dissection into the mediastinum farther than is possible under direct vision. The same procedure is then carried out on the second side. After the four parathyroids have been found, the enlarged gland or glands are removed totally. Before the incision is closed, it is most gratifying to have microscopic confirmation that the structure removed is actually a parathyroid adenoma.

In cases of wasserhelle hyperplasia all glands are involved. The diagnosis should be confirmed microscopically and subtotal resection of all parathyroid tissue carried out. A fragment of vascularized, viable tissue two to three times the size of a normal parathyroid is preserved to prevent tetany. This may prove somewhat difficult.

Carcinomas should be resected radically. In fact any parathyroid tumor which seems fixed to the thyroid or other structures should be resected without biopsy along with the surrounding tissues. Implantation and local recurrence are extremely common.

Mediastinal Dissection. I feel strongly, with Cope [9], that mediastinal dissection should not be carried out at the same time as a fruitless cervical dissection. In cases in which the adenoma is actually within the anterior-superior mediastinum, the three cervical glands should be found and identified by biopsy. The fourth gland should be proved missing by an extended search. This ideal may not be achieved, but in no other way can there be any certainty that the missing adenoma is actually within the mediastinum. The removal of normal or atrophic glands is useless and may lead to tetany when the adenoma is removed.

The dissection of the mediastinum should be postponed for a month or so. The persistence of hyperparathyroidism should be confirmed by appropriate tests since an adenoma may have been unknowingly destroyed or devascularized during the course of cervical dissection. The anterior-superior mediastinum is approached through a sternotomy incision, such as is used for thymectomy, and the same type of meticulous dissection should be carried out as was done in the neck. If an adenoma is not found, thymectomy is indicated.

The necessity for formal mediastinal exploration has arisen surprisingly rarely at the Clinic. In more than 250 proved cases only three mediastinotomies have been necessary to find and remove the adenoma, and in two of these, cervical explorations had been carried out previously elsewhere. Before deciding that the adenoma is in the mediastinum and before the cervical dissection is terminated, the surgeon should realize that in fact mediastinotomy actually is necessary in not more than 0.5 to 1.0 per cent of cases.

POSTOPERATIVE COURSE

In the usual case the values for calcium and phosphorus in blood and urine revert to normal within a day or so. In some cases, however, the concentration of phosphorus may remain depressed for weeks. This is particularly true in cases of osteitis fibrosa cystica. Not only does the concentration of serum phosphorus remain low but also the phosphorus in the urine practically disappears, which suggests that it is being used for skeletal repair. As mentioned previously, the sudden withdrawal of the hormone causes transient oliguria.

In the absence of osseous disease transient tetany occurs in about 50 per cent of cases. Treatment is usually not necessary. If all parathyroid tissue has been destroyed or removed, chronic tetany ensues which must be treated. If tetany sufficiently serious to require treatment does develop, treatment should be discontinued after several weeks in an effort to determine whether the tetany is transient or permanent.

In cases of advanced osteitis fibrosa cystica with markedly elevated alkaline phosphatase, a type of tetany, called "bone-hunger tetany" by Albright, develops after operation. Intensive treatment, including intravenous injection of huge quantities of calcium, may be necessary. The tetany persists until recalcification of the skeleton is well advanced. It is usually possible to control symptoms fairly well by intravenous administration of calcium lactate and by giving calcium and A.T. 10 or vitamin D by mouth.

Other postoperative complications are the same as those that develop after thyroidectomy. The recurrent laryngeal nerves are in even greater jeopardy than during thyroidectomy. Because of this I prefer to carry out cervical

dissection with the patient under local anesthesia. Intratracheal anesthesia is preferred by others.

PROGNOSIS

As far as is known, hyperparathyroidism resulting from adenomas and wasserhelle hyperplasia does not recur. The treatment of parathyroid carcinoma has proved most disappointing. In practically all cases the lesion has recurred locally or a functioning metastatic lesion has developed producing a recurrence of the hyperparathyroidism. Death usually has resulted from uncontrollable hyperparathyroidism and its complications rather than from the carcinoma.

The skeletal changes are completely reversible, that is, osteitis fibrosa cystica is cured. Gross deformities persist and the internal architecture of bones usually remains somewhat abnormal. True cysts do not recalcify. Osteoblastomas become hypercalcified. It is possible to diagnose healed osteitis fibrosa cystica roentgenographically by these changes. Of considerable interest is the fact that extreme pain and tenderness of the bones disappear within a few days or weeks, long before the skeleton has had time to recalcify to any degree.

The ultimate outlook depends entirely on the status of the kidneys at the time of treatment. Stones due to hyperparathyroidism do not continue to form; those resulting from secondary changes in the kidney, such as stasis and infection, may continue to form until the urologic cause is corrected. Of greater importance is the fact that renal impairment beyond a point as yet undefined is progressive in spite of cure of the hyperparathyroidism. If there is frank laboratory evidence of renal impairment such as azotemia or hyposthenuria, the condition probably will prove to be progressive. Death occurs, usually after ten to fifteen years, more commonly from the complications of hypertension than from renal insufficiency.

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DISCUSSION

Everett E. O'Neil (Boston, Mass.): Is there any discussion of this paper?

Question: I would like to ask Dr. Black if he finds peptic ulcers, that is the ulcers related to hyperparathyroidism, more common in women.

Dr. Black: I do not know. My impression, however, is that we do not. Osteitis fibrosa cystica is definitely more common in women than in men. I have the impression that lithiasis is more common in men. Actually in our series women still slightly outnumber men.

Question: I want to ask Dr. Black if dental x-rays have been used as a means of diagnosis.

DR. BLACK: Dental x-rays are of considerable importance in the diagnosis of osteitis fibrosa cystica. The lamina dura disappears. There is gross derangement of the internal architecture of bone. Giant cell tumors may be present and the undecalcified teeth serve as a nice index of the demineralization of the jaws. Actually, as you undoubtedly know, the diagnosis at present is largely chemical. Fully developed osteitis fibrosa cystica can be recognized as such roentgenographically. It was predicted some years ago that dental x-rays might serve to uncover cases of hyperparathyroidism. Actually few cases have been so found.

QUESTION: Have you had any cases in which the diagnosis has been suspected because of gastrointestinal symptoms? Can you classify the gastrointestinal symptoms which might alert us to the possibility of hyperparathyroidism?

DR. BLACK: There does seem to be some association between peptic ulcer and hyperparathyroidism. So far as I know, the ulcers respond rather poorly to treatment as long as the hyperparathyroidism persists. We have had a case or so in which the symptoms of ulcer practically disappeared after removal of a parathyroid adenoma.

The symptoms associated with hypercalcemia are, of course, pretty vague. They include loss of appetite, nausea, bloating and constipation. Actually the symptoms resemble those of purely functional states so closely that they have tended to confuse the diagnosis. We have attempted to carry out routine calcium determinations on patients with functional gastrointestinal complaints. We have uncovered no cases of hyperparathyroidism in the group.

QUESTION: Do I understand that these patients who are being screened are not all on a special diet, or are they?

DR. BLACK: No. The patients are not placed on any special diet before drawing blood for calcium and phosphorus determinations.

End of Symposium on Surgery of the Ductless Glands

Peptic Ulcer As a Surgical Problem

CLAUDE J. HUNT, M.D., *Kansas City, Missouri*

THE surgical treatment of lesions of the stomach and duodenum has been one of progressive change, an evolutionary process. Most surgeons a quarter of a century ago were supporting the procedure of posterior gastroenterostomy as the operation of choice in the treatment of peptic ulcer. Finney and Hanrahan [1], Judd and Hazeltine [2], Horsley [3] and others, however, were impressed with the results obtained by pyloroplasty. It was frequently employed by many surgeons.

Partial gastrectomy for duodenal ulcer was primarily initiated in Germany and Austria. It was used in preference to gastroenterostomy because fewer recurrent or stomal ulcers occurred.

A few bold surgeons in this country adopted this procedure and demonstrated a lower incidence of recurring ulceration after resection than was their experience following gastroenterostomy. Pioneers in this field of partial gastrectomy were Berg [4], Lewisohn [5] and Strauss [6], and their associates. Objections were widespread against removing such a large portion of the stomach for a small gastric or duodenal ulcer. Also, when a gastrojejunal ulcer did occur after resection, it was much more difficult to approach surgically than after gastroenterostomy and it required additional removal of the stomach. With the improvement of surgical technic, better understanding and evaluation of the surgical risk, proper preparation of the patient for operation and increasing experience with partial gastrectomy for ulcer, the operative mortality has steadily declined until now it is at a near minimum of 1 to 2 per cent.

It soon became apparent after experience and comparing results that resection was preferable to gastroenterostomy, and recurring ulceration was less frequent. The functional results were satisfactory. This is evidenced by patients who, then as today, after years of medical treatment for ulcer were restored to gastric comfort and an entirely new way of life following partial gastric resection. These patients report repeatedly that they regret not having submitted to the operation years ago. Comfort had been attained only by gastric resection. Serious complications, as compared to years of medical disappointment, have been so infrequent as to be no potent factor against surgery.

Vagotomy as revised and popularized by Dragstedt [7] has much merit and is a procedure of choice in many instances. Some surgeons advocate vagotomy with all gastrectomies, while others think radical gastrectomy is adequate and vagotomy has its place but not as a routine procedure in surgery for duodenal ulcer. This I will discuss later because I believe there are definite indications for vagotomy. If one desires it to be a routine associated procedure, I will not dissent. It is only by these different approaches that there will ultimately be a standardized procedure for and against associated vagotomy. Suffice it to say that no longer is gastroenterostomy or pyloroplasty an operation of contention, but gastric resection with or without vagotomy is the controversial issue. The procedure of partial gastric resection with or without vagotomy gives the lowest incidence of recurrence and the minimum of undesirable postoperative sequelae.

Replacement surgery is experimental. It

offers some advantage to the patient with the postgastrectomy syndrome but is associated with a higher incidence of ulcer recurrence. It is not an operation of primary choice and is rarely desirable in postgastrectomy complications.

INTRACTABLE ULCER

Intractable ulcer is a penetrating ulcer, usually on the posterior wall of the stomach or duodenum, which because of induration, fibrosis, vascular occlusion and crater formation is not likely to heal with any permanent degree of security under medical management. The lesion is comparable to a varicose ulcer of the leg, which heals with a thin, poorly vascularized epithelium. The blood supply is so poor that a well nourished granulation bed filling the exposed crater is impossible and nutrition is insufficient to promote permanent healing; hence an early breakdown is to be expected.

Surgeons believe that because of penetration, crater formation and insufficient blood supply for a granulating base, adequate epithelization will not result and healing will not be permanent. A patient with such an ulcer cannot carry on his normal activities, is intractable to medical management and should be operated upon.

Medical men state that these ulcers are not intractable. It is only the doctor or the patient who is intractable. They believe that comfort can be obtained by medical measures and that the ulcers will heal. How many people afflicted with such an ulcer can afford to subscribe to the required bedrest, diet and medical treatment? How long could one maintain good nutritional status under such a protracted regimen? How can he retain his economic responsibility and just how long would his zeal for such a restricted life exist?

We believe that with resection, postoperative gastric comfort can be largely expected, which is far more than can be obtained over a long period by medical treatment. The occasional unsatisfactory result after operation in no way compares to the uncertainty of long years of protracted medical management.

PERFORATED PEPTIC ULCER

The diagnosis of perforation is usually easy to make. If not confirmed by x-ray evidence of free air in the peritoneal cavity, acute pancreatitis must be considered. Many of the symptoms are similar and the presence of a high blood amylase does not confirm the diagnosis of acute pancreatitis or exclude perforation. The patient with perforated ulcer may have a high blood amylase from peritoneal absorption of escaped duodenal enzymes.

Air in large quantities injected into the stomach through a nasal tube may present a pneumoperitoneum on x-ray film if perforation is present which was not observed on the initial film. If no air is present by this method, there is no free perforation and immediate operation is not indicated. This procedure can do no harm. We have used it several times as a differential diagnostic agent.

Perforation of gastric or duodenal ulcer is considered by nearly all medical men as a surgical emergency. We know that when perforation occurs associated with either of these ulcers, there is an escape of gas and an outpouring of the contents of the viscus. Contamination occurs and serious infection may ensue. Some perforations are so slight that they may be spontaneously sealed by omentum or surrounding tissues. This has been repeatedly demonstrated at abdominal exploration. Only slight contamination and little or no infection of consequence occurs in these sealed perforations. Clinically the symptoms have been slight and usually unrecognized. When perforation is clinically apparent, we advise surgical exploration rather than gastric drainage and a medical regimen.

The problem of closure versus resection is controversial and to our point of view is related to whether the lesion is gastric or duodenal, obstructive or previously associated with hemorrhage.

Gastric ulcers which perforate should usually be resected at the time of exploration because of the uncertainty of the histological nature of the lesion. We have no means other than microscopic section to determine the cytology of the ulcer; and since at least 10 per cent of these gastric ulcerative lesions are malignant, resection rather than simple closure is advised.

This was dramatically demonstrated to me more than twenty years ago when I closed a supposed benign perforation of a gastric ulcer in a man thirty-nine years of age, to have him return six months later with an unresectable carcinoma of the stomach.

Perforation of a duodenal ulcer into the abdominal cavity may require simple closure, or certain conditions may indicate subtotal gastric resection. When there is no sign of ob-

struction, when the ulcer is not chronic, not extensively indurated near the pylorus, has not been intractable to medical management and has not bled, we believe the ulcer should be simply closed. Drainage should be employed if the duration of the perforation and abdominal contamination indicates. When in doubt, drain; it can do no harm. A perforation without induration or evidence of chronicity may remain symptomless after closure. Each case must be individualized. Some prominent surgeons have for years resected these lesions in most instances at the time of operation for perforation. We do, under the aforementioned condition.

MASSIVE HEMORRHAGE FROM ULCER

Massive hemorrhage is one of the major complications of peptic ulcer, and the decision to continue with medical treatment or institute surgical interference is hard to make. The medical and surgical viewpoints are often at divergent extremes. There must be a happy medium based upon the age of the patient, the degree of obvious arterial sclerosis, the patient's past history as to repeated hemorrhages and the response to a limited number of blood transfusions at the time of hemorrhage. Many papers have been written on this subject but no plan has been presented whereby a definite criterion would indicate immediate operation. The decision for operation is never an easy one to make. The tendency is, too often, to defer operation until vascular collapse is a problem of great magnitude.

We believe that in the presence of massive hemorrhage from peptic ulcer when circulatory balance is not restored after transfusions of 4 to 5 units of blood, the patient is still bleeding and operation should be instituted at once. We have never regretted this approach; and since some basis for action should be established, we believe this to be a workable plan.

Since most of these cases are seen first by the medical consultant, we believe that surgical advice should be promptly sought and an unbiased cooperative appraisal should be the basis of therapeutic action. We agree that bleeding often ceases spontaneously and many patients recover without operation. It is therefore hard to determine the procedure to follow in the individual case. We recognize, however, that the problem is real and that many patients die from massive hemorrhage from peptic ulcer who could have been saved by a timely operation. We would not consider operation for all patients with bleeding ulcer, nor would we condone medical management for all of them. Each case must be medically and surgically evaluated. We believe it is better to err on the side of surgery to stop the bleeding. We know from many experiences that these patients stand surgery remarkably well and that as soon as the bleeding is controlled the patient, who is in vascular collapse, will through transfusion support regain circulatory balance and a sustained blood pressure and become warm and pink. We advocate surgical cessation of the bleeding, with good expected results, even for those cold, pulseless patients with no blood pressure who are in extreme vascular collapse from hemorrhage. No other procedure is effective. The results well reward the surgeon for his courage and determined action. We often wonder why one ponders the wisdom of operation in these serious cases of hemorrhage when no such delay is considered in other similar surgical emergencies.

PYLORIC OBSTRUCTION—CHRONIC AND RECURRENT

Chronic pyloric obstruction represents the end result of a long-standing, progressively fibrotic constriction of the outlet of the stomach from ulceration. Some surgical procedure must be performed to provide an outlet for the passage of food if life is to be sustained. The choice of operation is, I think, dependent on the age of the patient and the acid values of the gastric contents.

For patients of advanced years with a relatively short life expectancy and low acid values, there is no better operation than posterior gastroenterostomy, with or without vagotomy (preferably without). If the patient has a long life expectancy and has high acid values, gastric resection is preferable. An accompanying vagotomy is a matter of individual preference. The ulcer is chronic, has long since run its course and the gastric values are usually not high enough to suggest an associated vagotomy.

Recurrent obstruction is preliminary to chronic obstruction. In all chronic fibrotic obstructions there have been previous episodes of this nature. Many patients with an ulcer near the pylorus get along fairly well under restricted activity and dietary precaution. They cannot, however, under normal activity escape periodic attacks of pyloric obstruction from

recurrent edema and activation of the ulcer. We therefore believe gastric resection should be advised after two or three trials with adequate medical management has failed to permit the patient to follow the way of livelihood for which he is prepared without recurring obstruction and discomfort.

CANCER AND GASTRIC ULCER

Much has been written about the relationship of acute gastric ulcer to malignancy. There is no accurate way to make a differential diagnosis, and he who treats a gastric ulcer for a protracted period of time without the realization that he may be dealing with a malignant ulcer is assuming a grave responsibility. There is no way of making an accurate diagnosis. The brush cytology method is excellent if positive but is of no value if negative. Response to treatment, the acid values of the gastric secretion, the diameter of the ulcer crater as seen by x-ray or the radiological indications of healing have not proved infallible. Even the gross appearance of the lesion after removal or multiple frozen sections at the operating table are often inaccurate. The location of the ulcer is of some value. Ulcers on the greater curvature are more frequently malignant than ulcers elsewhere. Those on the lesser curvature are less likely to be malignant than those in the prepyloric region of the stomach. Certainly there is a diagnostic error, based upon all known methods of differential diagnosis, of at least 10 per cent. We have 11 per cent and many have a much higher percentage.

Notable authorities as Welch and Allen [*8*], Marshall [*9*], Ravdin and Horn [*10*], Strode [*11*] and others confirm the high percentage of error in the preoperative diagnosis between benignity and malignancy in gastric ulcer.

ULCER HIGH ON LESSER CURVATURE

Ulcers high on the lesser curvature of the stomach are rare and are difficult surgical problems. High subtotal gastric resection, removing the entire lesser curvature, as in radical surgery for cancer of the stomach, can often be carried out leaving a good gastric pouch. We have not thought it advisable to perform total gastrectomy unless involved glands demonstrated cancer. We have not thought that gastrotomy with ulcer biopsy and frozen section accurately determined the true nature of the lesion. We therefore have not been content with such an uncertain histological biopsy finding to leave the ulcer *in situ* and carry out a distal gastrectomy. Hence we think that fundusectomy with esophagogastrostomy is the preferred operation if high resection cannot be accompanied with a segment of the fundus remaining as a food pouch. We have five cases in which we have performed fundusectomy with esophagogastrostomy, the esophagus being anastomosed to the distal end of the stomach accompanied with a sphincter pylorotomy. Esophagitis has not been a distressing factor in this small group.

GASTROJEJUNAL ULCER

When gastroenterostomy has been performed as a sole procedure and stomal ulcer develops, it is not sufficient to disconnect the gastroenterostomy and restore gastroduodenal continuity. Recurrence of the old duodenal ulcer will occur in 50 per cent of cases and in 60 per cent if pyloroplasty is performed, as reported by Walters [*12*].

When stomal ulcer develops in association with gastroenterostomy, the bypass should be disconnected and subtotal gastric resection should be performed. When recurrence has developed following subtotal gastrectomy, as mentioned under the discussion of vagotomy, a vagotomy should be carried out if no obstruction is present. The remaining stomach should be preserved if possible. Additional resection should be carried out only in the presence of an obstructive jejunal ulcer. If vagotomy is not successful, further resection can be performed subsequently.

REMOVAL OF ULCER

We believe that most ulcers can be surgically removed even when they are low, indurated and close to the common bile duct. We believe that any attempt to resect a duodenal ulcer should in all instances be accompanied with exposure of the common bile duct. This affords an appraisal of its relation to the indurated ulcer and an evaluation of the ability to close the duodenal stump securely after resection. We therefore know from experience with a large group of posterior penetrating duodenal ulcers that removal of the ulcer can usually be done. We disapprove of the exclusion operation. We believe it is unwise to leave the ulcer when it is possible to remove it. Although excluded from the erosive effects of the gastric juice, many ulcers may not heal or remain healed, as evidenced

by subsequent bleeding. I have always believed that the pathologic condition, when possible, should be removed.

DUMPING SYNDROME

The dumping syndrome is an objection to partial gastrectomy for peptic ulcer and is constantly presented as an argument against operation. It usually occurs during the meal or shortly thereafter. It is associated with weakness, pallor, often sweating and sometimes nausea and vomiting. In our experience it has not been a complication associated with any great degree of disability. A faint weakness is sometimes complained of; rarely is it disabling or permanent.

Presumptive theories concerning the origin of this condition are based upon the rather abrupt mechanical distention of the jejunal loop by the sudden dumping of the stomach contents into it—a solar plexus response.

I believe that too large a gastrojejunal stoma, the chemical factor of rapid undiluted hypertonic fluid being delivered in volume into the jejunum, resulting in the elevation of the blood sugar to a high level followed by a hypoglycemic reaction, is an important factor. It is therefore a hyperglycemic phase, followed in a period of time by a hypoglycemic one. I believe that the type of operation has a great deal to do with it. We are not bothered much with it since we perform the Hofmeister anticolic type of anastomosis and buttress the distal limb of the jejunum against the closed upper third of the lesser curvature of the residual stomach. We make a small stoma not over two fingers in diameter about the diameter of the jejunum, and with suture of the distal limb of the jejunum against the closed segment of stomach on the side of the lesser curvature, a valve-like outlet is made; thus the stomach cannot dump its contents into the jejunum suddenly and in great volume as it can in the Polya type of operation. This retarded emptying of the stomach can be well demonstrated by postoperative roentgenograms. In this anastomosis the proximal loop is placed at the greater curvature and the distal at the lesser curvature.

VAGOTOMY

The cephalic phase of duodenal ulcer and the complications of stomal ulcer after resection present the two types of ulcer in which vagotomy is most useful.

The gastric phase, accompanied with high gastric acidity, is controlled best through a lowering of the gastric acid by a high subtotal gastrectomy. Vagotomy is not essential. It is our policy to perform vagotomy in all cases in which there is a recurrent stomal ulcer without obstruction rather than perform another resection if the primary resection was adequate. Secondary resection can always be carried out, and we prefer to conserve the remaining stomach if possible. Our results have been good. The evaluation of vagotomy and gastroenterostomy is dependent on the period of time after operation. Walters [12] reports unfavorable results in 141 patients subjected to this procedure. Seventy per cent had good results, 25 per cent satisfactory results, and 5 per cent had recurrent ulcers in a follow up of 2.8 years; with the passage of further time the results were progressively poorer because of the more frequent occurrence of gastrojejunal ulcer, about 7 per cent. The frequency of recurring ulcer after radical partial gastrectomy has been about 2 to 3 per cent.

Vagotomy with posterior gastroenterostomy is the operation of choice when a patient is thin and a poor eater. A patient with this nutritional deficiency will never gain weight after resection. It is also a wise procedure in the case of duodenal ulcer associated with much edema and inflammatory reaction when it is apparent that closure of the duodenal stump might be insecure. A large amount of night secretion with high acid values, we think, indicates vagotomy associated with high gastric resection.

COLONIC REPLACEMENT IN SURGERY OF THE STOMACH

Replacements for segments of the stomach have been made by various splicing operations from portions of the intestinal tract. Moroney [13], in 1951 used a segment of the transverse colon to replace the distal end of the stomach in subtotal gastrectomy. The objective of this procedure was to prevent the symptoms of dumping and to provide more capacity for food intake in the hope of preventing weight loss. After this type of operation the patient can eat more, has relief of symptoms and there is a gain of weight. The dumping syndrome is abolished. These patients can eat fats and sugars as well as meats and have no steatorrhea and a normal glucose tolerance test. It would

appear to be a good operation but a formidable one, with an obvious increased mortality rate due to a prolonged procedure and multiple anastomoses.

Late in 1955 Moroney reported the recurrence rate as 8 per cent for duodenal ulcer when performed with vagotomy. Because of this high recurrence rate he has abandoned it in the routine treatment of duodenal ulcer. For those who have the postgastrectomy syndrome the results have been satisfactory with this procedure. There has been a gain in weight and slight postoperative sequellae. This procedure is inferior to high gastrectomy with or without vagotomy for duodenal ulcer because in no reported instance has the recurrence rate been as high as 8 per cent.

Watkins and Wittenstein [*14*] have used this procedure in seven cases. They believe that this makes possible a Billroth 1 type of reconstruction after subtotal gastrectomy. This is in reality a neo-stomach, and food is delivered slowly to the duodenum. The authors believe that the preservation of duodenal function is important from the standpoint of nutrition. No postgastrectomy syndrome was encountered. They advocate the procedure of subtotal gastric resection with colonic substitution.

JEJUNAL REPLACEMENT IN SEGMENTAL RESECTION OF THE DISTAL END OF THE STOMACH

In 1952 Henley [*15*] suggested segmental jejunal replacement of the distal segment of the stomach in resection for duodenal ulcer. He reported that this procedure eliminated the distressing features of the dumping syndrome, retained the normal duodenal relationship, maintained nutrition more satisfactorily and afforded a more adequate reservoir for food intake. Two years later he reported that none of the 130 patients had had the dumping syndrome and 96 per cent had gained an average of 14 pounds. Later, recurrent ulcer had developed in nine patients or 7 per cent. This is a high percentage of recurrence two to three years after any operation for duodenal ulcer—too high to justify the operation. It is over twice that associated with high gastric resection, and greater than that after gastroenterostomy and vagotomy. This procedure, like colonic replacement, is a formidable operation with an operative mortality rate much higher than that associated with subtotal gastric resection.

There seems to be no advantage in any kind of intestinal replacement operation in surgery of the stomach for duodenal ulcer that is superior to high gastric resection. In patients who have had high resections and have nutritional disturbance of grave import, restoration of duodenal continuity by a procedure of this type may be valuable. Intestinal segments to replace a portion of the stomach are too often susceptible to ulceration. The lower in the small intestinal tract the segment is taken for replacement, the more susceptible it is to ulceration. The nutritional value of replacement may be negated by its susceptibility to ulcer formation.

SUMMARY

1. The evolutionary procedures in the treatment of peptic ulcer are discussed step by step.

2. Intractable ulcer is a surgical problem. The surgical comfort far exceeds any that can be obtained by protracted and repeated attempts at medical treatment.

3. Recurrent obstruction finally must be corrected by surgical measures.

4. Perforation requires surgery and is discussed from the point of view of simple closure versus resection.

5. Massive hemorrhage is a controversial medical and surgical problem. Unbiased cooperation is urged. It is better to err on the side of early surgical relief than protracted medical observation.

6. Vagotomy is discussed as a routine procedure in gastrectomy. Our conclusion is that there are definite values to vagotomy and there is a useful field for its employment. Especially is it useful in patients with poor nutritional values, in low-lying duodenal ulcer, and in patients with high night secretion and high acid values.

7. The treatment of gastrojejunal ulcer associated with gastroenterostomy and gastric resection is discussed and a personal opinion is expressed. Resection in the former and vagotomy in the latter is recommended.

8. Intestinal replacement of a segment of the stomach by either a portion of the colon or small intestine is presented. Its merits and objections are noted. The procedure is not advised in the treatment of duodenal ulcer.

9. Attempts are made to discuss the problem from a practical point of view.

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Postgastrectomy Hemorrhage

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HEMORRHAGE following gastric resection is a serious, but little mentioned, complication. In order to describe our clinical experience with the handling of this type of hemorrhage, a series of 123 gastrectomies performed at this hospital since 1948 was recently reviewed. While mortality and over-all morbidity rates were similar to those of other reported series, a total of six cases of postgastrectomy hemorrhage occurred. This was the second most frequent complication, being exceeded only by superficial wound infections; it was at least a contributing factor in three of seven deaths, and necessitated three of thirteen secondary operations.

Postgastrectomy hemorrhage is mentioned briefly in most articles on the complications of gastric resection. Review of the literature, however, shows few published articles dealing specifically with the prophylaxis and treatment of this complication. Rothenberg [*1*] reports a collected series of 975 gastrectomies with an over-all incidence of 1.54 per cent. Gutman [*2*], in an analysis of mortality in a collected series of 3,747 gastrectomies performed in V. A. hospitals, reports twelve deaths from postoperative hemorrhage. It is generally reported that the complication occurs between the first and fifth postoperative days but it may occur immediately following gastrectomy. It has been reported as late as the fourteenth day. The over-all incidence is reported as between 1 and 3 per cent [*1–4*].

Postgastrectomy hemorrhage in this report is defined as any bleeding in the postoperative period which requires 500 cc. or more of blood replacement. It may be associated with either the original disease or with failures in operative technic. Despite the custom in this hospital of making a detailed study of hemorrhage factors for bleeding patients, no case of hemorrhagic diathesis was discovered as the underlying cause for hemorrhage.

The following are abstracts of the six cases of postoperative gastrectomy bleeding in this series. It should be emphasized that these patients were operated upon by various residents in the department; however, they were all the direct responsibility of one surgeon (W. A. C.).

CASE REPORTS

CASE 1. P. D., a forty-two year old white man, entered the medical service on July 29, 1954, with a four-year history of pain from a duodenal ulcer. He was placed on a rigid medical regimen, but on August 17, 1954, he began to have melena and hematemesis. Because this occurred while on good medical treatment, he was transferred to the surgical service on that day. He was operated upon immediately and the ulcer was found to be posterior, with extensive scarring and invasion of the pancreas. Hofmeister subtotal gastrectomy was performed, but the ulcer was not resected. Postoperatively, the patient continued to pass some blood in the stool and required transfusions on several occasions. His blood volume, however, could be maintained and reoperation was not considered necessary. On the seventh postoperative day severe abdominal pain and abdominal rigidity developed. He was reoperated upon and the gastrojejunal anastomosis, which was found to be disrupted anteriorly, was repaired. On the day following the closure of the disruption, the patient suddenly began to vomit blood and required transfusion for shock. His gastric tube became occluded by clots, and he vomited large rope-like masses of blood which were approximately 2 inches in diameter and as much as 1½ feet in length. These tough clots would block the pharynx to the point where they would result in involuntary aspiration of blood into the trachea. He was given a transfusion and again operated upon. The duodenal

stump was opened and found to be filled with clotted blood. Before any further surgery could be performed the patient died. At autopsy, blood was found in the pulmonary tree, and the gastroduodenal artery was open at the base of a large ulcer crater.

This case points to a peculiar clinical finding which was explained by the autopsy. It could be demonstrated that the stomach and duodenum were filled with long, tough, rope-like clots, and that these had resulted from the clotting of the blood in the proximal loop as it was lost from the artery at the base of the ulcer. This should have alerted the clinicians to its place of origin. This type of clot directly resulted in death since this patient's lungs were filled with aspirated blood.*

CASE II. J. S., a thirty-seven year old white psychotic man, had vegetated for six months previous to admission. He entered the medical service on May 14, 1956. For nine years he had been diagnosed as having Wilson's disease (hepatolenticular degeneration). He also had a proved duodenal ulcer for nine years, with six previous upper gastrointestinal hemorrhages. On this admission, the patient had been having melena and hematemesis for three weeks; he entered in shock. His temperature on admission was 105°F., presumably from hepatic failure. He was given transfusions, but on May 16, 1956, he was still actively bleeding. The patient was therefore transferred to the surgical service where laparotomy was performed. The liver was found to be small and consisted primarily of scar tissue. The duodenal ulcer was posterior and densely adherent to the pancreas and common bile duct. Hofmeister subtotal gastrectomy was performed but the ulcer was not removed. The patient did well postoperatively, except that he could not cooperate in coughing because of his semicomatose condition. On the third postoperative morning his gastric tube was removed. At 2:00 P.M. he became quite distended. The gastric tube was reinserted. At 4:00 P.M. the tube drainage became grossly bloody. His bleeding soon became profuse and he was given multiple rapid transfusions. The hemorrhage failed to stop and he died at 8:00 P.M. At autopsy, a large vessel was seen protruding from the base of the ulcer crater.

CASE III. S. M., a forty-two year old white man, had previously undergone vagotomy and gastroenterostomy. He was admitted to the medical service on April 1, 1954, with epigastric pain. This failed to respond to medical management and he was transferred to the surgical service. On April 15, 1954, a Billroth I type of gastrectomy was performed. The jejunum was resected proximal and distal to the gastroenterostomy and anastomosed end-to-end with a one layer aseptic anastomosis. The stomach was then resected and anastomosed to the duodenum. No definite ulcer was found. On the third postoperative day the patient began to have massive melena which consisted of dark blood with some bright red blood. He had no hematemesis. His hemoglobin dropped to 9.5 gm. On proctoscopy, his colon was found to be filled with dark blood. He was given 2,000 cc. of whole blood and the bleeding stopped spontaneously and did not recur. His further postoperative course was uneventful. Because the bleeding occurred late, consisted of melena only, was relatively slow and no blood appeared in the gastric aspirate, it was assumed that its origin was the end-to-end, one-layer, jejunal anastomosis.

CASE IV. D. H., a fifty-five year old white man, had intractable pain from a previously diagnosed duodenal ulcer. He was treated intensively by conservative means, but failed to respond. On December 23, 1952, subtotal Hofmeister gastrectomy was performed. The patient tolerated the procedure well. At 6:00 P.M., on the evening of the operation, his gastric tube drainage became grossly bloody. His blood pressure dropped to 60/0 mm. Hg. Transfusions were started and he received a total of 2,000 cc. of whole blood. The gastric tube repeatedly became occluded with large clots in spite of frequent irrigations. He frequently vomited around the tube and aspirated blood into his lungs. The bleeding had not subsided by 10:30 P.M. and he was taken back to the operating room. The anesthesiologist was able to remove a large amount of the previously aspirated blood. The gastrojejunal anastomosis was opened. Several bleeding points were found and individually ligated. The patient had no

* Dr. E. M. Phillips of Wheeling, West Virginia, in a personal communication, reported an additional case in which these peculiar rope-like clots were encountered. His case required reoperation and the clots were found to be issuing from the afferent jejunal loop. They were, in effect, casts of the jejunum.

more bleeding and his further postoperative course was uneventful. The cause of bleeding in this case was considered to be inadequate hemostasis at the line of gastrojejunal anastomosis.

CASE V. J. W., a fifty-nine year old white man had severe asthma and pulmonary emphysema. He entered the medical service on April 7, 1956, with a history of three episodes of hematemesis and one tarry stool shortly before admission. His bleeding subsided promptly after admission. An upper gastrointestinal series revealed duodenal ulceration. On April 16, 1956, he again began to have melena. During the following three days his hemoglobin dropped from 14 gm. to 9.5 gm. and the melena continued despite intensive medical treatment. He was transferred to the surgical service on April 19, 1956. On April 20, 1956, the patient underwent Hofmeister subtotal gastrectomy. The duodenal ulcer was located anteriorly. The ulcer was not actively bleeding on inspection and it was not resected. On the first postoperative day, he had an asthmatic attack, and his wound disrupted during the course of his severe coughing. A secondary closure was performed under general anesthesia. On April 23, 1956, he began to have massive hemorrhage of bright red blood through his gastric tube. Despite repeated lavage of the gastric tube, it frequently became occluded with clots. During this period he vomited around the gastric tube and aspirated blood into his lungs. He was given multiple transfusions but the bleeding continued, and on April 24, 1956, he was again taken to the operating room. The stomach was entered through the line of the previous anastomosis. Many large clots were removed. No active bleeding point due to a large artery was found, although several points of bleeding were seen along the mucosal suture line where it had been partially disrupted by distention of the stomach. High on the posterior wall of the gastric remnant, however, was a small punctate area from which arterial blood issued in considerable quantity. It was considered that this was the most likely source of the postoperative hemorrhage. Considerable discussion failed to elucidate whether or not this had been present at the original operation. Following this operation, status asthmaticus and pneumonia developed. The patient was bronchoscoped repeatedly, and on May 10, 1956, tracheotomy was performed. His asthma was treated intensively but failed to respond. He died on May 12, 1956.

CASE VI. C. K., a thirty-nine year old white man, was admitted to the medical service with a ten-year history of pain from a duodenal ulcer. For two years he had had intermittent pyloric obstruction. Surgery was recommended, and on February 2, 1952, he underwent subtotal Hofmeister gastrectomy. An anterior duodenal ulcer was found, with marked pyloric obstruction. The ulcer was removed. At 11:00 P.M., on the night of surgery, his Wangensteen drainage became quite bloody. He had an increase in pulse rate and a drop in blood pressure. He was given 500 cc. of whole blood. His pulse and blood pressure stabilized and, by the following morning, his Wangensteen drainage was clear. No further bleeding occurred and his further postoperative course was uneventful. The site of bleeding was never determined.

COMMENTS AND CONCLUSIONS

Of these six patients, two bled postoperatively from gastroduodenal arteries at the base of posterior, penetrating ulcers which had been left in place at the time of gastrectomy. Two patients bled from anastomotic suture lines. Of these two, one bled from inadequate hemostasis of the stomach wall and the other was presumed to have bled from a jejunojejunostomy suture line of the aseptic type. A fifth patient bled from a punctate ulcer high on the upper wall of the stomach, which was considered to have been overlooked at the time of the original surgery. In the sixth patient, the cause of hemorrhage was never determined.

As illustrated by the first two case histories, a vigorous attempt during gastrectomy for bleeding duodenal ulcer should be made to deal directly with the bleeding point. Statements frequently appear in the literature that simple gastrectomy will cause cessation of bleeding from duodenal ulcer. The first and second cases presented indicate that this is not necessarily true. Although actual resection of the ulcer is not considered necessary, some definitive treatment of the bleeding point in the ulcer bed is mandatory. There are numerous descriptions in the literature of technics which will accomplish this objective [6–9].

Cases III and IV illustrate the necessity of careful hemostasis during gastrectomy. An

open type of anastomosis lends itself most readily to good hemostatic technic [5]. In Case III, a jejunojejunostomy was performed by closed aseptic technic, over clamps. Although there are many advantages and indications for an aseptic type of anastomosis, this case illustrates the inherent dangers of any technic which does not allow direct visualization and individual ligation of bleeding points. In Case IV, however, anastomosis was performed by the open method, and still there was bleeding from the gastric suture line.

Case V illustrates the fact that, even though a duodenal ulcer is present, some other lesion may actually be a source of hemorrhage. During gastrectomy, if blood is not actually seen issuing from an ulcer crater, a thorough search should be made for additional sources of bleeding.

Authors are at variance as to the proper course of action when a postoperative hemorrhage occurs. Some recommend conservative treatment with sedation and blood replacement. Others favor early reoperation [5]. We believe that the treatment should be individualized in much the same manner as that for any upper gastrointestinal hemorrhage. Blood replacement should be prompt and adequate. Reoperation should be considered if blood volume cannot be maintained or if the bleeding has not subsided after an adequate attempt at conservative management. A special problem exists in cases in which intragastric clots form and make it difficult to keep the stomach empty. In these patients, a large gastric or Ewald tube should be substituted for the ordinary small-lumen gastric tube. This will often allow lavage to be accomplished. If lavage is not adequate and drainage is not continuous, the stomach quickly becomes distended and causes undue tension on suture lines. This may cause further bleeding. Another danger of inadequate drainage is vomiting around the gastric tube, with aspiration of blood into the pulmonary tree. This unhappy chain of events is considered an indication for immediate reoperation in this hospital.

The technic of reoperation also varies. Rothenberg recommends gastrotomy above the gastrojejunal anastomosis so that the suture line may be observed [1]. We have found it satisfactory to carefully enter the stomach through the line of the previous anastomosis. After the suture line has been examined, if blood is not seen issuing from the afferent jejunal loop, the entire gastric mucosa is inspected for ulceration or erosions. If this procedure fails to locate a bleeding point, then the duodenum must be examined. This may be performed with equal ease either by reopening the duodenal stump or through a separate duodenotomy incision.

SUMMARY

Postoperative hemorrhage following gastrectomy is a serious and not uncommon complication about which little has been written. Six cases have been presented with a brief review of the literature. The mortality was 50 per cent in this series. The causes of postoperative hemorrhage have been listed and conclusions drawn regarding prophylaxis and treatment. One of the most important findings from this series was the fact that three patients bled postoperatively from lesions which were not removed at the original operation. Two of these lesions were posterior penetrating duodenal ulcers, with hemorrhage from an open gastrodeuodenal artery, and the third was an overlooked, punctate ulcer of the stomach.

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Open Tibial Shaft Fractures—Immediate Soft Tissue Closure

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The background of this presentation is a review of the records of 147 patients admitted to Harlem Hospital with open tibial shaft fractures, unilateral and bilateral. Procedures for immediate closure of the soft tissue wounds were employed with significant success. This series, covering a period of five years from 1952 to 1956, inclusive, includes 117 single tibial shaft open fractures and thirty cases of bilateral shaft fractures, one or both shafts compounded, representing a total of 157 soft tissue wounds.

TYPES OF FRACTURE

Single Tibial Shaft Open Fractures. Statistical data on the 117 cases of single tibial shaft open fractures are presented in Table I. The anatomical location of the fractures and the open wounds are also tabulated, the majority of the soft tissue wounds being on the anterior medial border. In twelve patients in this group infections of the superficial and deep tissues developed, and there were three cases of osteomyelitis.

Forty of the 117 patients had other injuries or fractures, the gravity of which resulted in fifteen deaths, with cerebral injuries and irreversible shock the most frequent cause of death. There were no fatalities from overwhelming infection or complications directly associated with the open tibial fractures.

Fourteen patients left the hospital at their own responsibility after reduction of the fractures and closure of the wounds, but before the expiration of the optimal observation period for such injuries. The remaining eighty-eight patients were adequately followed up and repeated examinations demonstrated satisfactory results in healing and function.

Bilateral Tibial Shaft Open Fractures. There were thirty patients with injuries to both lower extremities, including forty open tibial shaft fractures. Table II presents pertinent data on these cases. In this group of patients also, the soft tissue wounds appeared more frequently on the anterior medial border. Healing was delayed in five cases by infection in the superficial and deep tissues, and there were three cases of osteomyelitis.

There was a high incidence of associated trauma, with twenty-six of the thirty patients having other fractures or injuries. Five of these

Table I

STATISTICAL DATA ON SINGLE OPEN TIBIAL SHAFT FRACTURES

Total number of patients			117
Total number of open tibial shaft fractures			117
Sex incidence:			
Females			26
Males			91
Associated fractures or injuries			40
Position of tibial shaft fractures:	Upper third	Middle third	Lower third
Right	11	29	17
Left	7	18	24
Segmented fractures	12	..	..
Position of wounds:			
Anterior and medial borders			90
Lateral borders			27
Complications:			
Superficial and deep wound infection			12
Osteomyelitis			3
Results:			
Surgery, adequately followed up (recovered)			88
Surgery, inadequately followed up (patient signed out at own responsibility)			14
Deaths from associated injuries			15

patients died from cerebral injuries and shock. Follow-up examinations of the remaining twenty-five patients were continued for periods sufficient to establish their recovery.

In many instances it was difficult to interpret the area of the wounds from descriptions

TABLE II
STATISTICAL DATA ON BILATERAL OPEN TIBIAL SHAFT FRACTURES

Total number of patients			30
Total number of open tibial shaft fractures			40
Sex incidence:			
Females			8
Males			22
Associated fractures or injuries			26
Position of tibial shaft fractures:			
	Upper third	Middle third	Lower third
Right	4	12	13
Left	5	14	10
Segmented fractures	2	..	..
Position of wounds:			
Anterior and medial borders			30
Lateral borders			10
Complications:			
Superficial and deep wound infections			5
Osteomyelitis			5
Results:			
Surgery, adequately followed up (recovered)			25
Deaths from associated injuries			5

TABLE III
SIZE OF WOUNDS IN OPEN TIBIAL SHAFT FRACTURES (GREATEST LENGTH IN ONE DIRECTION)

Total number of patients	147
Total number of open tibial fractures	157
Wounds ¼ to 2 inches	62%
Wounds 2 to 4 inches	30%
Wounds 4 to 8 inches	5%
Wounds longer than 8 inches and large defects and avulsions	3%

in the records. It was thought that a better concept of the size of the wound could be gained from a consideration of its greatest length in one direction. This measurement varied from ¼ inch to wounds longer than 8 inches. There were also wounds representing large defects in or avulsions of the skin. The incidence of wounds of various lengths is presented in Table III.

TREATMENT

The closure of open fractures of the tibial shaft presents difficulties that are not encountered in the management of injuries to the other long bones of the extremities. The tibia may be visualized as triangular in shape throughout its length, with an anterior crest or apex. The apex and medial borders are devoid of muscle and the subcutaneous tissue is scanty. On the lower third of the tibial apex and medial borders, the subcutaneous tissue is often absent and the skin is thin [1] and inelastic. The thinness of the soft tissue and its reaction to injury make closure difficult and sometimes impossible.

On the other hand, the lateral and posterior borders of the tibia are covered by a thick pad of muscle and subcutaneous tissues, which are conducive to the closure of defects in this area. However, they often interfere with closure on the opposite borders. The dynamic action of the tibial shaft muscles is unbalanced in the normal leg and, when the bone is fractured, this imbalance is greatly exaggerated. The dynamic action of the muscles may cause the bone fragments to override, to angulate or to displace in the direction of the wound on the apex or medial border. This muscular force at the site of the wound is considerable. Pressure of the bony fragments obstructs the immediate closure and later, during the healing period, may be a factor which invites disruption, devitalization or necrosis of the soft parts.

Compere [2] indicates two primary principles in managing the soft tissue parts of the open fracture. The first is to convert the open fracture into a closed fracture. The second encompasses the time factor or the so-called "golden period." If surgery is necessarily postponed for six to eight hours, it is better to close the wound later by delayed or secondary closure. We do not extend the time of immediate closure beyond six to eight hours. The majority of our open fractures are closed within three hours.

There are substantial reasons why immediate wound closure is advantageous: (1) the soft parts heal within fourteen to twenty-one days; (2) repeated contamination of the wound is avoided; (3) induration and scarring are minimized; (4) repeated dressings are unnecessary; (5) ambulation is earlier; (6) hospitalization is shortened; and (7) medical cost is held to a minimum.

In an open fracture, several preliminary steps are required before closure is attempted, and successful closure is dependent upon their careful execution. Discussion of the details in each

step is unnecessary here, but some elucidation of primary principles is included.

For the sake of brevity, the preliminary steps are divided into three parts, namely, the ambulance phase, the emergency ward phase and the operating room phase. The battle for effective and permanent closure may be won or lost in any of these stages.

The Ambulance Phase. It is here that the open fracture is first observed. Usually management entails the control of three vital factors: (1) the control of hemorrhage; (2) the prevention of further contamination; and (3) the fixation of the extremity for transportation.

The Emergency Ward Phase. During this period the entire organism is appraised and evaluated. Physiological and chemical deviations are corrected. The integrity of other vital structures and organs is determined. Antibiotic therapy is instituted to inhibit bacterial proliferation and invasion. We do not propose to discuss treatment in detail, but it would not be amiss to say something about antibiotics in general.

The effectiveness of antibiotics, when properly used, has been phenomenal. They have changed our entire concept and approach to the management of the open fracture. Until the advent of these drugs, the sulfa group included, most immediate closures of any size failed. In many instances following closure, the extremity or life itself was threatened. Antibiotics represent the therapeutic advance which, as an adjunct to sound surgical principles, makes possible the successful conversion of the open fracture into a closed fracture. We like to think of antibiotics as a farmer utilizes weed killers. The farmer must work his soil just as diligently as ever if he wishes a good vigorous crop, and the surgeon must always depend on meticulous and sound surgery for a permanent closure *per primam*. Antibiotics, here as elsewhere, may not be substituted for sound surgery.

The Operating Room Phase. This phase in the management of the open tibial fracture is divided into two distinct parts, namely, debris surgery and reconstructive surgery.

In debris surgery, the objectives are to clean or prepare the extremity, to remove devitalized and disorganized tissue by débridement, and to explore the wound.

We attempt by débridement [3] to convert a ragged contaminated puncture, laceration or avulsion as near as possible to a clean surgical wound. All flayed and macerated muscle tissue is incised until live and bleeding tissue is observed. Fascia that is tattered and shredded is removed. Special attention is devoted to fascia that has been detached from underlying structures. Bony fragments which are attached to muscle and periosteum by substantial tissues are left *in situ*. Bony fragments held by threads of tissue or lying free in the wound are treated as free grafts. Preservation and conservation of the skin is important and only a thin rim of skin around the wound is removed by sharp dissection.

The wound is explored simultaneously for lacerated nerves, large blood vessels and tendons. The fractured bone is visualized.

Before, during and after débridement the wound is irrigated with a considerable volume of sterile saline solution.

Every open fracture does not necessitate extensive débridement. Small puncture wounds and lacerations require only the excision of the skin edges and devitalized skin. We have also observed that a small skin laceration on the muscle borders does not indicate the extent of damage to the deeper structures. Clinical experience and clinical judgment will dictate whether such a wound should be enlarged and inspected.

The objectives of reconstructive surgery are: (1) the repair of vital structures, blood vessels, nerves and tendons; (2) the reduction and immobilization of the fracture in the simplest possible manner; and (3) the closure of the skin without tension.

The Fractured Bone. The fractured bone may be passive or dynamic. The passive or stable fracture need only be reduced and the fragments hooked when possible. After closure of the wound, a long leg cast is applied. In the majority of cases, this is sufficient.

The dynamic or unstable fracture must be reduced and retained. We prefer to institute the simplest method possible for retention or fixation. The device used for this purpose should be introduced as far as possible from the open wound. We employ the following methods: (1) traction through the os calcis; (2) intramedullary nailing [4–6]; (3) the two-pin method incorporated in plaster; and (4) plaster body cast.

Each open fracture must be evaluated and the best method for treatment instituted for

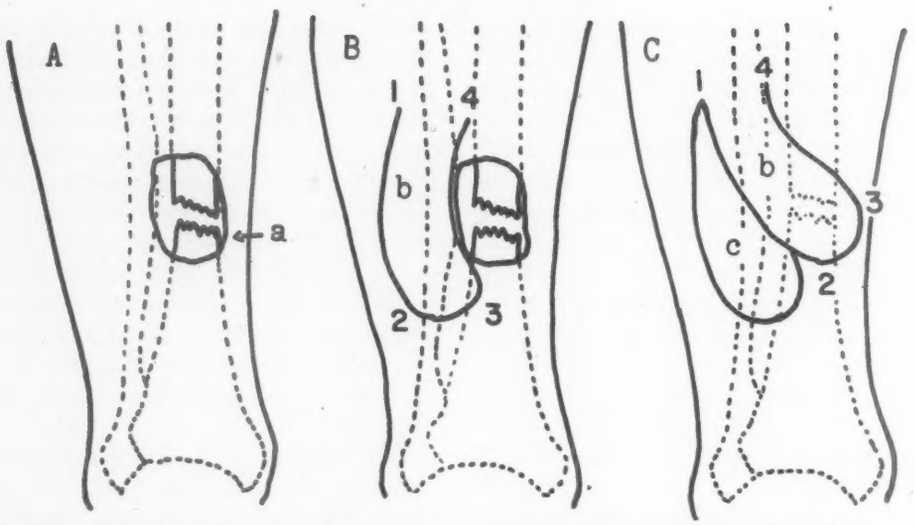


FIG. 1. A, showing soft tissue defect (a) (skin and subcutaneous tissue) at site of fracture. B, showing outline of unipedicled flap (b) (skin and subcutaneous tissue) to cover traumatic defect over fracture site. C, showing transfer of flap (b) to defect. The area (c) represents the defect left after transfer of flap. This area is covered by a free partial-thickness skin graft.

the individual case. We are not satisfied with the reduction until overriding of the fragments is corrected and the pressure on the wound from within is counteracted.

In the desperately injured patient [7] there are other considerations. Time-consuming procedures are not tolerated and must be abridged or abandoned in favor of more expeditious therapy. In a few serious cases, time permits only sterile dressings to the wound and the encasement of the limb in plaster splints. At a later date the wound not healed may be closed secondarily and the fracture reduced under more propitious circumstances.

Closure of the Soft Tissues. The closure of the wound is usually reduced to closure of the skin. The soft parts are brought together with interrupted sutures at certain salient points or angles. Most of the soft tissues readily fall in position as the skin is closed.

Tension is one of the greatest hazards to effective wound closure. The length of the laceration or diameter of the wound seems to have little relation to healing if tension and infection are avoided. To eliminate tension, some type of skin graft may be indicated.

Since free skin grafts will not remain alive when applied to exposed bone, which is akin to laying a graft on a foreign body, the surgeon must resort to the use of pedicled flaps for closure in these cases. Such flaps may be obtained from tissue adjacent to the defect (local or contiguous flaps), as shown in Figures 1 and 2, or from tissue remote from the defect (distant flaps), as depicted in Figure 3 [8,9]. We prefer, wherever possible, to use local flaps. The reasons for this choice are the following: (1) No immobilization of the uninvolved parts of the body is required. (2) In multiple injuries, fixation of other parts to the fractured limb may be impossible or disadvantageous. (3) In elderly patients, due to changes in the joints, it may be difficult or impossible to approximate the other leg or an upper extremity to the injured tibia. (4) In employing flaps from a distance, the position for the proper application of the flap may not be the best position for proper bone alignment.

Because transfer must be immediate, these flaps cannot be delayed to improve and assure their blood supply prior to application to the defect. It is therefore necessary to assure blood supply by using broad pedicles and, wherever possible, more than one pedicle. Our preference is for bipedicled sliding flaps. (Fig. 2.) The base on which the flap is to rest must be so treated that no projections are present to cause pressure on the flap. In cases in which there is much scarring of the fractured leg from previous trauma, or when the remaining normal tissue is insufficient to cover the defect, flaps from a distance must be employed.

When there has been avulsion of large masses of skin and soft tissue, impairing the viability

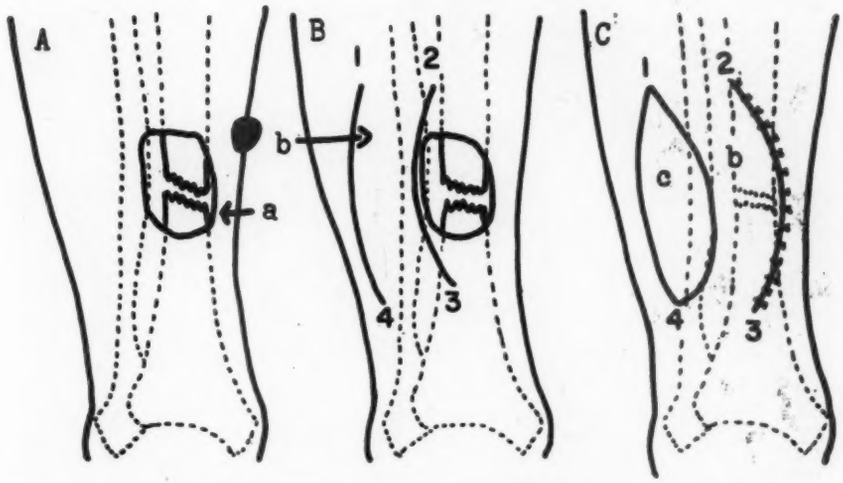


FIG. 2. A, showing defect (a) resulting from loss of soft tissue. B, showing the formation of a bipedicled (skin and subcutaneous tissue) contiguous flap (b) between points 1,2,3,4, elevated from the underlying tissue. C, showing the flap (b) transferred over the defect. The area (c) represents the defect left after transfer of the flap. This area is covered by a free partial-thickness skin graft.

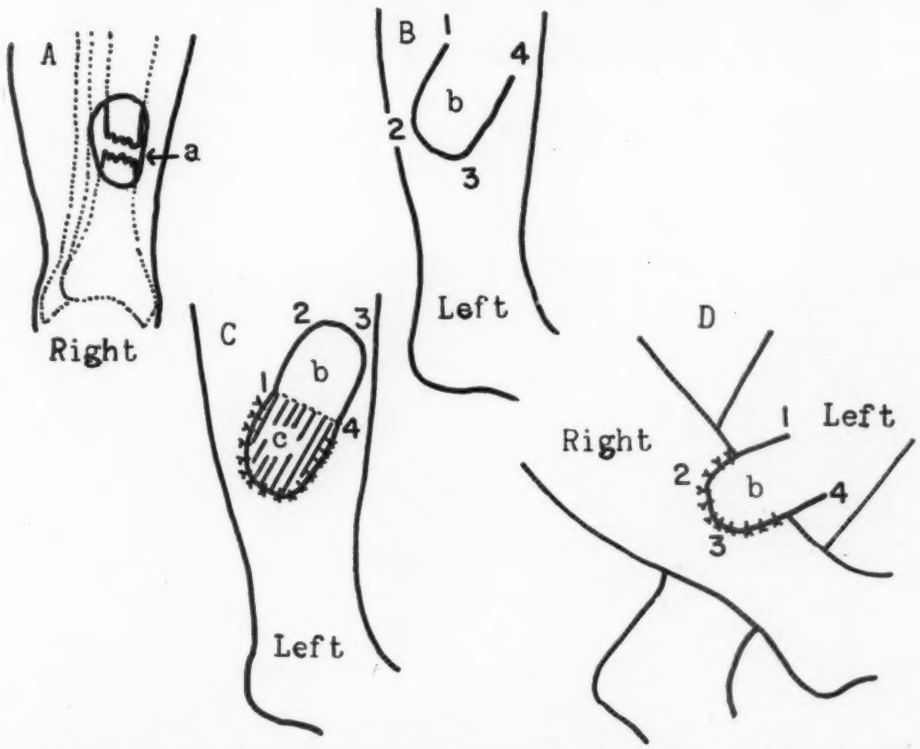


FIG. 3. A, showing soft tissue defect (a) of right leg. B, showing outline of flap (b) between points 1,2,3,4 of left leg. C, showing flap (b) elevated and defect resulting, covered by free skin graft (c). D, showing flap (b) applied to defect of right leg and sutured.

of these tissues, the use of the skin of such flaps as free grafts is a very worth while expedient [*10*].

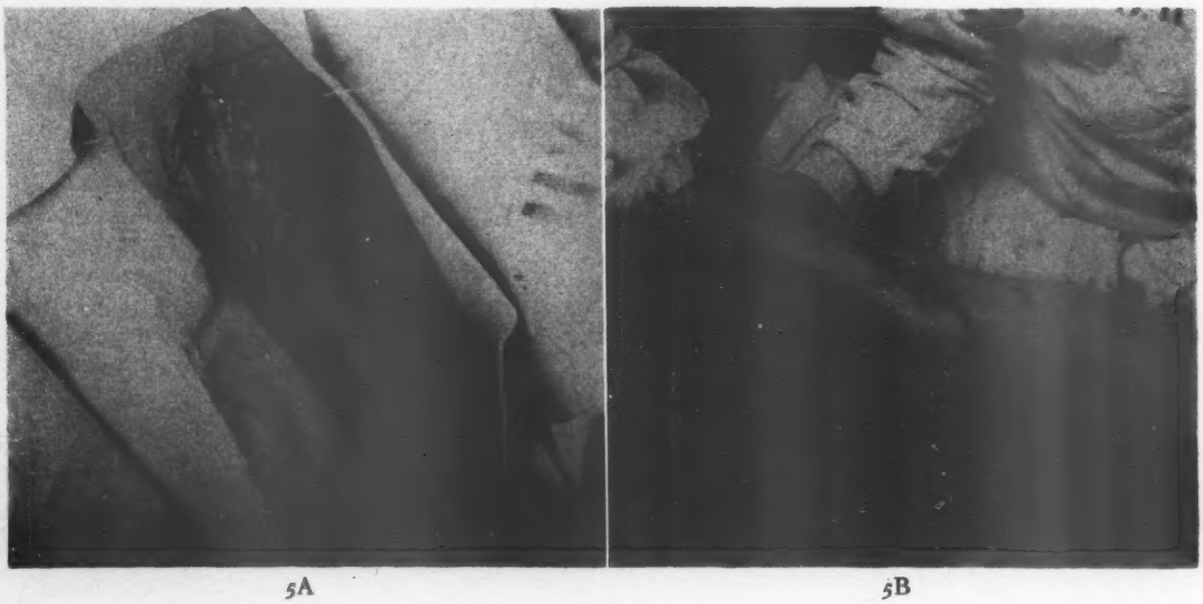
The following cases illustrate the application of these principles.

CASE REPORTS

M. V. (Case No. 54-10151), a twenty-five year old woman, fell from a third floor window on June 12, 1954, sustaining multiple injuries, among which was an open fracture of the left tibia. There was a

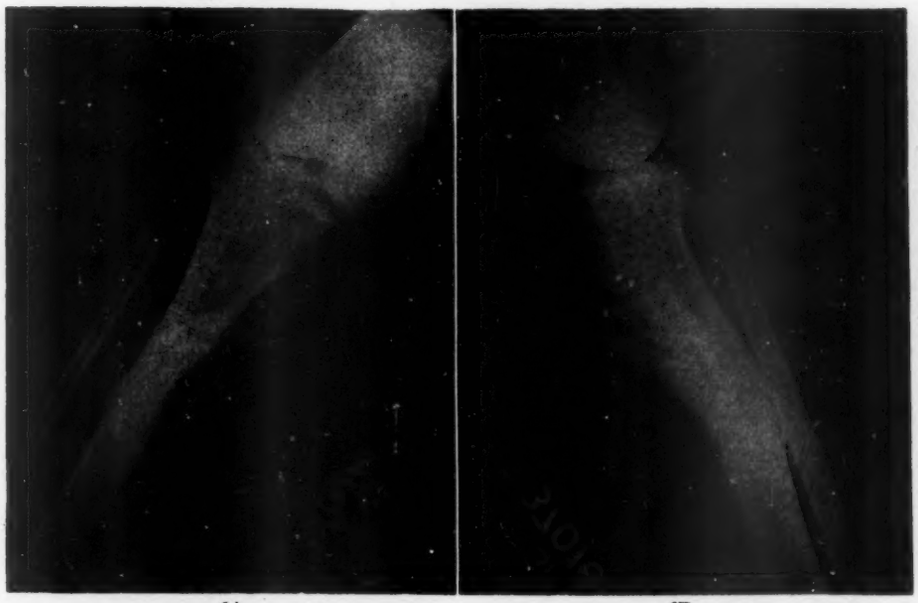
4A 4B

FIG. 4. Patient M. V., June 12, 1954. Comminuted, compound fracture of the upper third of the left tibia. A, anteroposterior view. B, lateral view.



5A 5B

FIG. 5. Patient M. V., June 12, 1954. A, soft tissue wound over compound, comminuted fracture of the upper third of the left tibia, prior to surgery. B, following immediate closure of the soft tissue defect with a bipedicled contiguous skin flap. The donor site posteriorly was covered with a free skin graft.



6A 6B

FIG. 6. Patient M. V., December 31, 1956. X-ray showing bony union of comminuted fracture of the upper third of the left tibia, eighteen months post-trauma. A, antero-posterior view. B, lateral view.

7A 7B

FIG. 7. Patient M. V., twenty-two months post-trauma. A, showing healing of soft tissue defect closed with a bipedicled contiguous skin flap. B, showing healing of donor site from which a bipedicled skin flap was taken for closure of anterior soft tissue defect. Donor site originally covered with a free skin graft.

soft tissue defect on the anterior lateral aspect of the left leg, in the upper third, measuring 14 cm. by 5 cm., in which there were fragments of bone, shredded muscle and debris. Figure 4A and B delineates the fracture of the left tibia and Figure 5A shows the soft tissue defect.

After the patient's cardiovascular and respiratory systems were stabilized and shock was controlled, the wound was irrigated copiously with normal saline and débrided. The loose fragments of bone were reposited in the wound. A bipedicled contiguous flap, having a length-to-breadth ratio of two to one and one-half, was raised medially and transferred over the defect and sutured *in situ*. A free skin graft was used to cover the defect left posteriorly after transfer of the flap. (Fig. 5B.) The extremity was immobilized in plaster.

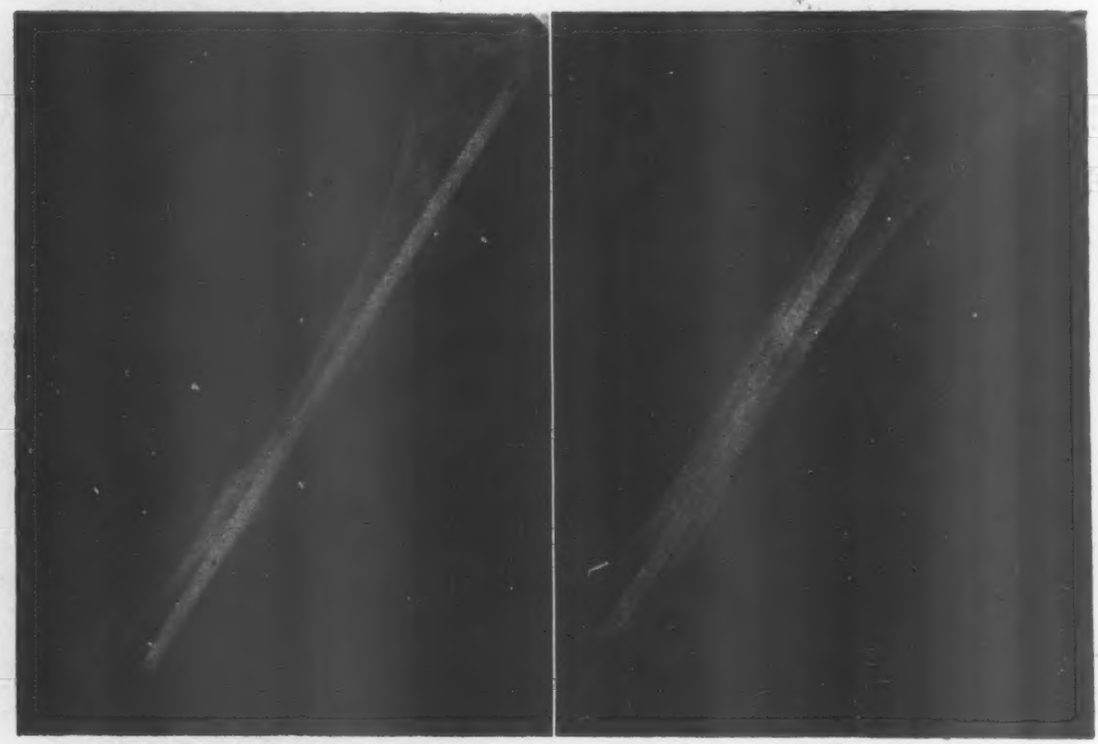
Healing of the flap was by first intention, except

8A 8B

FIG. 8. Patient W. W., April 18, 1953. Double fracture of the left tibia. Distal fracture compounded. A, antero-posterior view. B, lateral view.

9A 9B

FIG. 9. Patient W. W., April 18, 1953. Comminuted, compound fracture of the lower third of the right tibia. A, anteroposterior view. B, lateral view.



10A 10B

FIG. 10. Patient W. W., August 6, 1954. Intramedullary nail *in situ* and callus formation in double fracture of the left tibia, sixteen months after injury. A, antero-posterior view. B, lateral view.

for an area of 7 by 3 mm. at the center of the anterior border of the flap. This healed by secondary intention.

Callus formation was minimal six months after injury and for this reason the bone was drilled at the fracture site. Subsequently, callus formation was slow but progressive. Eighteen months after injury bony union was complete. (Fig. 6A and B.) The healing of the soft tissues is demonstrated in photographs taken at twenty-two months. (Fig. 7A and B.) When last seen in February, 1957, the patient had returned to work.

W. W. (Case No. 53-6764), a forty-four year old man, was struck by an automobile on April 18, 1953. In addition to fractures of the pelvis, he had open fractures of both tibias. There was a double fracture of the left tibia. (Fig. 8A and B.) The proximal fracture was in the upper third of the shaft and comminuted. In the distal third of the tibia there was an open fracture with division of the soft tissues over two-thirds of the circumference of the leg. Examination of the right leg showed an open fracture of the lower third (Fig. 9A and B), with avulsion of soft tissues, resulting in a defect 4 inches long and 1 inch in width on the anterolateral aspect of the leg. There were multiple old and recent scars of the leg, the results of previous trauma.

After stabilization of the patient's cardiovascular system, the skin around the wounds was cleansed with pHisoHex® and the wounds were irrigated with normal saline and débrided. Intramedullary nails were inserted into each tibia through incisions in the proximal portions of the bone.

The skin of the left leg was closed without tension except for a triangular area medially, the base of which consisted of healthy subcutaneous tissue. A free split-thickness graft was applied to this area.

Because of the abundant scarring of the right leg, the use of a bipedicled sliding flap was considered inadvisable. A unipedicled flap, having a wide base, was developed on the lateral aspect of the leg, rotated into the defect and sutured to the margins of the wound. The denuded area resulting from the rotation of the flap was covered with a split-thickness skin graft. Both extremities were immobilized in plaster.

There was a partial thickness loss of the flap in its distal inch. After separation of the necrotic layer, the flap healed spontaneously.

Examination seven months after injury showed no soft tissue defect of the left leg. Callus formation was seen on x-rays of the left leg after ten weeks, but did not appear on x-rays of the right leg until five months after injury.

The patient was discharged on December 24, 1953, eight months after injury. Firm bony union was demonstrated in the left and right tibias by x-rays at sixteen and nineteen months, respectively. (Figs. 10A and B and 11A and B.) When last seen in the Follow-up Clinic after three years, bony union was present and there was no soft tissue defect.

11A 11B

FIG. 11. Patient W. W., November 12, 1954. Intramedullary nail *in situ* and bony union of fracture of the right tibia nineteen months post-trauma. A, anteroposterior view. B, lateral view.

IMMEDIATE POSTOPERATIVE CARE

Four objectives are paramount in postoperative care. The first is to correct any existing severe anemia with whole blood; second, to correct electrolyte imbalance; third, to correct nutritional defects; and fourth, to control infection through antibiotic therapy.

We use one of the broad-spectrum antibiotics, tetracycline or oxytetracycline, 250 mg. four times daily for seventy-two hours [*11*]. The continuance of antibiotic therapy is governed by the temperature chart. Penicillin is administered only in the emergency ward, 600,000 units on admission.

Roentgenographic studies are made at frequent intervals.

The wound *per se* is undisturbed, except for elevation of the extremity. To fuss and fumble with the wound is meddlesome surgery. In the absence of any indication to justify it, the wound is not inspected unless an open reduction is contemplated to correct malalignment of the fracture.

SUMMARY

Data are presented on 147 patients with open tibial fractures, unilateral and bilateral, involving 157 wounds. Two typical cases, in which the wounds were closed with bipedicled flaps, are reported.

The basic principle and objective of the management of an open fracture is its conversion into a closed fracture. The injured person and the open wound should receive sound surgical attention from the time of injury until the closure of the wound. The patient should be evaluated and every deflexion from the normal should be corrected as soon as possible. The open wound itself should be brought under control as far as hemorrhage, debris and reinfection are concerned. The wound should be converted from a dirty, contaminated wound with devitalized tissue, to a surgical wound, thoroughly débrided and with tissues adequate in circulation. Antibiotics must not be substituted for good surgical principles, as their function is ancillary to surgery. The soft tissues, other than the skin, are best left unsutured, except at salient points or angles. Fragments of bone, stripped of their periosteum and blood supply, may be left in the wound where they may serve as free grafts and scaffolding for new bone if adequately protected against infection by antibiotic therapy and skin covering. One of the greatest deterrents to wound closure is tension, which may be overcome by appropriately placed relaxing incisions or pedicle skin flaps.

Every effort should be exerted to close the open fracture as soon as possible and as completely as possible.

CONCLUSIONS

At Harlem Hospital, since the advent of antibiotics, our experience with open fractures of the tibial shaft and a review of the literature leads us to emphasize that skin covering for the open fracture is of the greatest importance. It offers the best protection for the other soft tissues and the bone. Primary closure prevents repeated reinfection and promotes both soft tissue and bone healing.

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Vaginal Plastic Surgery Based on a New Concept of the Anatomy of the Female Genital Tract

IV. THE ANORECTAL BIRTH INJURIES*

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MODERN obstetrics has largely eliminated the anorectal birth injury, but it still occurs. It has occurred as a complication of median perineotomies.

The immediate or intermediate repair of this by the obstetrician is a commendable effort, but it is not always crowned with success. Many such patients will eventually seek relief in the gynecological clinics. However, even the gynecologist is not pleased with the ultimate results.

A study of textbooks with reference to anorectal injuries leaves one with a sense of depression and frustration. It would seem that an impasse has been reached in the therapy of this condition; there is a pervading air of defeatism. Only one operative procedure is described which has been copied from book to book for many years. Unfortunately, it is strikingly inadequate and futile.†

Is the situation really so hopeless that no further effort is to be made to offer a better solution to this perplexing problem? I am not convinced of this, and therefore have developed the following basic principles: (1) The treatment of anorectal injuries must be concentrated on the re-establishment of normal anatomic conditions of the anorectum, disregarding entirely, for the time being, the perineal pathology. (2) Since this birth injury affects a part of the intestinal tube, in order to be rational and successful the treatment must make use of certain well established principles of intestinal surgery. (3) It is essential to bear in mind that the pathologic anatomy varies greatly with the duration of the lesion. Therefore, the surgical treatment must be varied and adjusted to the conditions as they present themselves. It is illogical to have just one method of approach when so many variables are constantly encountered. In other words, the treatment of old lacerations and their associated complications must be different from the treatment of fresh or relatively recent ones.

† In a recently published book on gynecology, a scant page is devoted to the text of the operation, with a few illustrations on the next page. It is most disappointing since it is one of the best books on the general subject of gynecology.

PATHOLOGY

Two phases must be recognized concerning the physical state of the tissues involved.

Pbase 1. This refers to the fresh or relatively recent lesions, i.e., within a few months after delivery. In this phase, the lesion presents itself as a triangular cleft in the rectovaginal wall. The apex of the triangle constitutes the extent of the rent up the rectovaginal wall while the torn ends of the external sphincter are discernible at each angle of the base of the triangle. At this stage, the torn ends of the sphincter muscle are not very far apart from each other.

Pbase 2. This concerns the old, neglected lesions and those patients who have been operated upon unsuccessfully. Marked changes in the physical state of the involved tissues have taken place.

As a result of contraction and retraction of

* Parts I, II and III appeared in the May, July and October 1957 issues, respectively, of *The American Journal of Surgery*.

the involved musculature and the added inflammatory elements incident to this condition, the triangular cleft, previously mentioned, has undergone considerable changes. The lower end of the posterior vaginal wall is now represented by a straight, transverse line. (This is well illustrated in all textbooks.) There is a widening of the vaginal orifice due to retraction of the torn ends of the sphincter muscle. There is also a considerable shortening of the posterior vaginal wall.

As a result of the inflammatory changes, there is a marked scarring of all the tissue elements. The torn ends of the sphincter muscle are no longer visible or even recognizable as they are now buried in a mass of scar tissue. It will also be observed that all tissue elements are dry, hard, indurated and even friable; in some cases they are almost cartilaginous in consistency.

Both these phases are the result of the same lesion, but are very different when the element of time becomes a factor.

GENERAL PRINCIPLES IN TREATMENT

The sphincter apparatus of the anorectum is a rather complicated structure, but so far as the present topic of discussion is concerned, its chief elements are the internal sphincter muscle and the external sphincter muscle.

The Internal Sphincter Muscle. This is an involuntary muscle. It is not an independent muscle, but consists of the circular fibers of the rectal muscularis in the lower end of the anorectum, where it is considerably thickened as though it were reduplicated on itself. This muscle is under the influence of the sympathetic nervous system.

The External Sphincter Muscle. This is a voluntary muscle. It is a distinct, independent muscle—a broad band surrounding the lower end of the anus and under the influence of the central nervous system.

(The levator ani muscle cannot be considered a sphincter of the rectum. If the rectal sphincter is cut accidentally or intentionally in operations for fistula *in ano*, the patient becomes incontinent; the levator muscle, although intact, does not control the incontinence. The levator muscle is a voluntary muscle and could hardly be expected to contract all the time to preserve continence.)

It must be realized and fully appreciated that certain conditions, when present, are inimical to favorable operative results. These are: (1) When the tissues involved are dry, hard and indurated, sutures will cut through and the wounds will not heal. (2) When so much contraction, retraction and scarring of the tissues has taken place that the triangular cleft into the rectovaginal wall (previously mentioned) has been converted into the straight transverse line, the tissues become unyielding and immobile. They cannot be brought together to their proper place unless force is used, but this will lead to failure in any operative procedure. That is particularly true with reference to the torn ends of the external sphincter muscle. If the torn ends are brought together under too much tension, they will probably come apart before the patient is off the operating table.

What, then, should be the method of treatment in such cases? A course of preliminary treatment must be instituted. The object and the principles of such treatment must be thoroughly explained to the patient in order to get her confidence and cooperation. Then, good judgment on the part of the surgeon will determine when the condition of the tissues has become suitable for surgical treatment.

THE PRELIMINARY HOME TREATMENT

The patient should be instructed in the use of frequent bowel irrigations, especially after each evacuation. This will reduce the amount of soiling and minimize irritation by intestinal secretions.

Then, daily warm sitz baths must be taken. The beneficial effects of sitz baths cannot be overestimated; dry, hard, scar tissues will gradually become soft, supple and pliable.

Office treatment with boroglycerine tampons is extremely helpful. This brings about a softening of the tissues and helps in the absorption of the inflammatory elements. At the same time, the patient should be seen at frequent intervals so that the surgeon can estimate her progress.

If, however, in spite of persistent and conscientious treatment there is no evidence of any improvement in the tissues, then it will become necessary to resort to drastic procedure, even though this is bound to be met with considerable resistance. This is where the principles of intestinal surgery come in. Nothing less than a preliminary, temporary colostomy should be performed. This procedure is particularly applicable to patients who have been

subjected to surgical repair without any success. In these cases so much necrosis and sloughing of the tissues has taken place that there is hardly enough healthy tissue left with which to work. The temptation to "try it just once more" is great but is just as likely to result in complete failure again, and may even permanently and hopelessly cripple the patient.

By sidetracking the fecal current, the lower bowel becomes "bacteriologically defunctioned," so that the future operation will be performed in practically an aseptic field.

While the colostomy is functioning, the inflammatory condition in the rectovaginal wall will gradually subside; the induration will disappear; the tissues will become soft, pliable and easily mobilized so that the parts can be brought together without any tension. The sutures will not cut through and satisfactory healing will take place.

The effect of these preliminary treatments will become manifest more promptly and the operative treatment may be undertaken much sooner, undoubtedly with more confidence as to the results. Incidentally, the patient can take better care of herself with the colonic stoma than she is able to with an incontinent rectum.

After undergoing colostomy the patient is sent home, where she will keep up the treatment as regards the sitz baths. The office treatment is also to be continued.

SURGICAL TREATMENT

Assuming that the patient has had the proper preliminary treatment, and the condition of the tissues to be dealt with has improved to the extent that a favorable outcome may be expected, then, and only then, may the patient be sent to the hospital for surgical treatment.

In the hospital (provided no colostomy was required) the patient is kept on a low residue diet for a few days. At the same time, bowel irrigation and sitz baths are continued as she had been doing at home.

Attention should be paid to the general condition of the patient. If anemia is present a blood transfusion may be indicated. Antibiotics, tonics, etc., are given according to the surgeon's preference.

OPERATIVE PROCEDURE

The operative procedure to be described consists of two parts, not two separate or stage operations. The one operation is divided into two sections, due to the character of the tissues to be dealt with.

PART I. The vagina is irrigated with normal saline. A piece of iodoform gauze is inserted into the rectum to prevent soiling of the operative field during the operation.

Technic: The transverse border of the vaginal orifice is freshened and all scar tissue is excised. Only fresh, viable, bleeding tissue is of any use in this repair work.

The vaginal wall is then separated from the rectal wall for about 2 cm. all around. The torn ends of the external sphincter muscle are immediately sought and a temporary suture is passed through each end. The suture lifts up each end and an attempt is made to approximate them in the median line. This converts the wound into a somewhat triangular form, simulating the original triangular cleft observed immediately after delivery. If the tension is too great, some dissection and freeing of the torn ends from the scar tissue will be necessary.

Traction is then made with an Allis clamp on each border of the wound to determine whether or not the two sides can be brought together without any tension. There must be no tension. This cannot be stressed too much nor too often. If there is no yield to the tissue, further separation of the rectal wall from the vaginal wall must be performed. There is plenty of rectal wall to be drawn upon no matter how much may have been destroyed. When sufficiently free and readily yielding, closure of the wound may be undertaken.

A fine silk suture threaded on an intestinal needle is passed from the vaginal surface, about 1 cm. above the apex of the triangular cleft, into the rectum. The needle is removed and a clamp is applied to the rectal end of the suture and left hanging under the drapings. Any other instruments used are discarded.

The surgeon changes gloves.

The vaginal end of the suture is threaded into another intestinal needle. Now, a number of longitudinal bites are taken alternately, on one side, near the border of the wound and then on the other side until the skin is reached. The skin is not penetrated. The suture takes in only the rectal muscularis; the mucosa is carefully avoided.

The ends of the suture are picked up, the suture line tightened, the suture tied, and the cut ends left long, about 5 cm. from the knot.

The iodoform gauze is withdrawn from the rectum. The drapings are removed and all instruments are discarded. The vagina is again irrigated with normal saline to remove clots, debris, etc.

The surgeon, his assistants and the nurse change gowns and gloves, and the patient is redraped as though being prepared for a new operation.

PART II. The rectum has been excluded. The surgeon is now working in a more or less aspetic field. Reference has previously been made to the presence of the internal sphincter muscle, and it was also stated that it is not a separate muscle but a constituent part of the circular layer of the rectal muscularis. In closing the rectal wound, as previously described by bringing the sides together, the torn ends of this muscle were naturally included. An additional suture, however, will reinforce the primary (silk) suture and will assist in the complete reconstruction of this sphincter. This is done as follows:

Starting in the lower end of the wound and using a small full curved needle threaded with a fine chromic suture, a deep bite is taken in the thickened part of the muscularis on each side of the primary suture, and the suture is tied. The suture is then continued upward, which inverts and also reinforces the primary suture.

Suture of the External Sphincter Muscle: It is now necessary to bring about the union of the torn ends of the external sphincter muscle.

The temporary sutures previously left on each torn end of the muscle are picked up, and the ends are brought over toward the median line and anchored there with a mattress suture of chrome gut. The temporary sutures are removed.

It would not be safe however to depend upon this suture alone. As stated on previous occasions, the absorbable suture gets soft, soggy and loose in the presence of the tissue juices, and in this case the powerful contractility of this muscle may then pull the ends apart, resulting in the complete failure of the whole procedure. To prevent this calamity an additional figure-of-eight mattress suture of silk or silkworm gut is added. It takes in each side of the muscle and the ends of the suture are brought out through the skin and left untied temporarily. This suture when tied takes the tension off the primary suture and splints it at the same time. This suture should never be omitted.

A very important structure, the perirectal fascia, must then be looked for and taken care of. It may have become exposed in the wound by this time, but more likely has not. Therefore, it will be necessary to further separate the vaginal wall from the rectal wall until the fascia is finally found.

The silk or silkworm gut suture on the external sphincter muscle is now tied and the fascia is sutured in the median line over it.

The vaginal wound is still open but is to be taken care of in connection with the perineorrhaphy, which is to follow.

This completes the operation for the repair of the anorectal birth injury. It will be observed, as indicated from the very outset, that this condition has been considered and dealt with as an isolated lesion of a part of the intestinal tube, and that the perineal pathology had been completely ignored, for the time being, as if it were non-existent. It is my conviction that, with this mental attitude toward the treatment of anorectal birth injuries, better operative results will be achieved in the future.

POSTOPERATIVE TREATMENT

The patient is kept on a low residue diet. The bowel is left severely alone. On the fifth day and daily thereafter, a small dose of mineral oil is given twice daily; the patient is quite likely to have a spontaneous, soft bowel movement in a day or two.

Enemas should be avoided, unless the surgeon himself, or his most trusted associate is willing to perform that function. Under no circumstance should this function be delegated to the mercy of a pupil nurse. A slight thrust of the rectal tube in the wrong direction may ruin everything.

On the sixth postoperative day the primary, rectal, silk suture is cut on the vaginal side of the knot and is left there for a few days; there is no harm in waiting. The suture becomes loose, and the rectal end, the knotted end, is picked up with a clamp and is pulled out without causing the patient the slightest pain.

The figure-of-eight skin suture is cut and removed when it appears loose, usually on the tenth or twelfth postoperative day.

Phlegmasia Cerulea Dolens

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Presented at the Annual Clinical Session of the American College of Surgeons Second District Chapter of Texas, May 11, 1956, Corpus Christi, Texas.

PHLEGMASIA cerulea dolens is a form of thrombophlebitis of the lower extremities in which there is fulminating venous thrombosis accompanied with marked reflex arterial spasm and by varying degrees of shock. The arterial spasm is so extreme that a diagnosis of arterial embolism is frequently made. Because it appears to be, in all its manifestations, more like an arterial embolus than a thrombophlebitis, it is frequently called "pseudoembolic phlebitis." Other names for this condition are "blue phlebitis of Gregoire," "gangrene of venous origin," and "acute massive venous occlusion of the extremities." Fifty per cent of these cases progress to gangrene and amputation of the extremity, and one-third end in death. After study of the recent and historical background of this condition, I am firmly convinced that the majority of cases are going unrecognized and are probably mistaken for ordinary thrombophlebitis or phlebothrombosis.

History. In 1593 Fabricius Hildanus was the first man to recognize the possibility of gangrene of venous origin in the extremities. In 1859 and 1894, cases were reported by Hueter and Gaillard. As a clinical entity the condition was described by Tremolières and Veran in 1929 and by Gregoire in 1938. There were only three case reports in the American literature until DeBakey and Ochsner [3] reported two in 1949. Oaks and Hawthorne [13] in 1948, and Young and Derbyshire [20] in 1950 reported recovery following ligation of the vena cava. Sympathectomy was not performed in these cases. In 1951 Miles [11] reported a case, to bring the total up to sixty. He used clot removal, ligation with No. 4 silk, division of the vena cava and sympathetic blocks. Many cases have been reported since 1951, and perusal of the literature reveals a definite difference of opinion as to therapy. More emphasis should be placed on early diagnosis and treatment because of the morbidity as well as mortality associated with phlegmasia cerulea dolens.

Clinical Manifestations. Phlegmasia cerulea dolens differs from phlegmasia alba dolens in that the onset is more sudden and the symptoms more severe. The distinguishing features are a violaceous discoloration of the skin of the affected extremity, accompanied with diminished or absent arterial pulsations and with temperature and sensory alterations. Edema of the leg, thigh and lower trunk is obvious. Lastly, shock of varying degree always accompanies this condition. Of the four cardinal symptoms and signs of the disease—pain, coldness, collapse and cyanosis—the only sign of venous origin is the rapid onset of edema. Haimovici [5] states that phlegmasia cerulea dolens is preceded in approximately 44 per cent of the cases by phlegmasia alba dolens. It may occur within a few days or after several weeks, and in 56 per cent of the cases it is the initial manifestation. The edema is glossy, tense and woody. Cyanosis is rapid to more distal parts first, then becomes absent. The anoxic manifestations are followed in four to eight days with gangrene. Multiple venous occlusions do occur. Of twenty-seven cases reported, two revealed both legs involved.

Pathological Physiology. The profound circulatory disturbance simulates arterial occlusion, but pathologic study of amputated legs and necropsy specimens has revealed a patent arterial system with associated complete occlusion of the venous channels. The sudden shock in this condition can probably best be explained on the extravasation of serum into the leg, thigh and lower trunk on the affected side. Death in approximately one-third of the cases is considered to be due to profound circulatory collapse. Transient cyanosis and ischemia may

occur. Blue phlebitis does not necessarily lead to gangrene, but if present the gangrene is generally moist in type. It appears in the most distal parts as a superficial bluish discoloration. Blebs and lymphangitis appear with poor demarcation, and with infection added the typical picture of wet gangrene is obvious. In approximately two-thirds of the cases the distal arteries are not palpable. The lower extremities are affected four times as frequently as the upper extremities. According to DeBakey and Ochsner [3], pulmonary embolism occurs in 10 per cent of the cases.

Etiology. Fontaine and Pereira [4] have shown that gangrene could be produced in animals only when the venous return was completely blocked. Veal et al. [19] studied the effect of massive venous occlusion on the arterial blood flow in experimental work on dogs. The mesenteric vein was ligated and continuous pressure recordings were made. The cardinal signs of acute massive venous occlusion were produced. Blood flow came to a standstill when venous pressure reached its peak. The only chance for arterial blood to enter was in the replacement of fluid lost in the tissues. Ochsner and DeBakey [14] believe that the most plausible explanation of the condition is simple blockage of the circulation by the thrombosis. The fact that the condition progresses to gangrene in spite of antivasospastic measures indicate that vasospasm does not play the primary role in the genesis of the condition. It may follow postpartum thrombophlebitis, chemical thrombosis, phlebothrombosis with a shifting thrombus of the vena cava, external or femoral vein ligations, postoperative ulcerative colitis, complications of surgery, trauma, visceral malignancy, Buerger's disease, polycythemia vera or infection. The production of this syndrome depends not only on the amount of obstruction but also on the suddenness of occurrence.

Therapy. More recent reports continue to advocate conservative therapy directed toward the prevailing abnormal physiological process. Since venous engorgement is prominent, Veal [19] and his associates have proposed and utilized with good results marked elevation with manual active exercise to the involved limb to express blood from the involved limb mechanically. Others have reported good results with novocain® injections of lumbar sympathetic nerves and ganglia. Vasodilator drugs are advocated, and in the opinion of Davis and Grimes [2] anticoagulant therapy is the preferred method. Even though previous reports have shown that ligation of the vena cava is dramatic in its effect, some of the later writers have stated that it should not be done unless pulmonary infarcts occur. It is the belief of most writers that anticoagulant therapy helps the collaterals. Transfusions of whole blood or plasma should be given immediately in those cases in which shock is present. Morphine is necessary to relieve the pain.

It is difficult to select the best type of treatment, since good results have been recorded with either conservative measures or operative procedures. Miles [11] emphasized the physiological response following ligation of the vena cava. Shock disappeared and pulsations in the peripheral vessels returned to normal within a very short time. This excellent response could not be attributed to the spinal anesthetic, because the effect would have been noticed soon after the anesthetic was given, and not thirty or forty minutes later when the ligation was done. Ray and Burch [15] reported that vena cava ligation induced diminished pulsations, and it is a paradoxical physiological response that the pulsations return to normal or become palpable immediately after ligation of the vena cava. The variation in treatment somewhat confuses or disguises the effect of vena cava ligation. Only by recording each individual case with immediate observation of the extremity following ligation will we be able to determine how consistent are the excellent effects. Ligation in this condition is done primarily to prevent pulmonary embolism, as clinically most cases reveal the thrombus to be well into the common iliac vein and devoid of inflammatory element.

It is thus apparent that one can combine all the principles of logical therapy, namely, early recognition and treatment with ligation of the vena cava, lumbar sympathectomy, anticoagulants, antibiotics, moderate elevation, moderate active exercise and compression bandages when the patient is allowed out of bed. Blood replacement is essential to prevent death from circulatory collapse.

CASE REPORT

R. D., a sixty-three year old white man, was seen for the first time at his home on March 15, 1956, at approximately 1:15 P.M. Examination

revealed him to be apprehensive but in good spirits. He gave a history of having been on his feet the day before, and that he had had a certain cramping pain in the right calf at approximately 10:00 P.M. the night before. He gave a history, also, of having had thrombophlebitis in the left leg approximately twelve years previously. He had had no acute pain since then, but did have occasional swelling of the left leg if he was up very long. He first noticed pain in the left calf and swelling of the left thigh and leg at 8:00 A.M. on the day he was first seen. The symptoms grew in severity, and he became increasingly restless and apprehensive. When seen his face was ashen gray and wet with perspiration and his skin was cold and clammy. He complained of severe pain in the left leg. There had been no chest pain, dyspnea or hemoptysis. His temperature was normal and his pulse was approximately 130, weak and irregular. The left lower extremity was cold, wet, diffusely edematous and reddish blue in color. The left dorsalis pedis artery and posterior tibial and left popliteal pulsations were so diminished that it was questionable whether any of them could be palpated. Tenderness was present over the course of the left femoral vein. There was a positive Homans sign on the left.

By the time the patient could be gotten to the hospital, with the preoperative diagnosis of a possible saddle embolus extending into the left common iliac artery, he was much worse clinically and the degree of shock was more profound. The blood pressure was 70/40 and pulsations had completely disappeared from the left lower extremity. Shortly before he was taken to the operating room it was again possible to palpate, with some question of being positive that minimal pulsations were present in the left groin and left posterior tibial artery. The anesthetist believed that the addition of shock required immediate transfusion, because of the extravasation of serum into the greatly swollen left thigh and leg. This was done immediately following administration of a spinal anesthetic. Precaution was necessary not to overload the patient, since his past history revealed two coronary attacks several years previously. An electrocardiogram and x-ray of the chest were within normal limits preoperatively.

A long midline incision in the lower abdomen, extending four or five fingers above the umbilicus to the symphysis pubis, was used to expose the contents of the abdominal cavity. On exposing the retroperitoneal area it was obvious that there was no embolus in the aorta or in the common iliac arteries. The pulsations were present but diminished, and the appearance of the vessels was that of vasospasm. The sigmoid colon was reflected medially, and the posterior parietal peritoneum opened to be reflected along with the ureter in a medial direction across the psoas muscle. This exposed the lumbar sympathetic chain on the left which was resected, and the second, third and fourth sympathetic ganglia which were excised. After this, the belief that an embolus was still present distal to the common iliac artery almost suggested an exploration distal to the inguinal ligament. However, before this was done, the veins were exposed and a large clot was found lying in the left common iliac vein as it was crossed by the right common iliac artery. This area was not visible until the fat and areolar tissue were removed, which were even more difficult to expose in this case because of the edema present in the tissues. When the left common iliac vein was exposed, it was found to contain a thick, elongated, heavy clot extending distal to the point where it was compressed by the right common iliac artery. Proximal to the artery, an examination of the vena cava and the right common iliac vein revealed no evidence of clotting. Without disturbing the clot and without opening the vein, umbilical tape was passed about the lower edge of the vena cava, which was ligated in continuity. Only enough of the vena cava was exposed to permit this ligation. A gallbladder clamp was used to free the area behind and around the inferior vena cava, and the umbilical tape was drawn beneath the vena cava and tied in place. As it was tied, the patient's general condition was checked. The blood pressure and pulse did not change with the first application of the suture. Therefore the tape was left in place since it did not seem to disturb his general condition. However, from the time the vena cava was ligated and the wound was closed with interrupted cotton sutures, examination of the foot revealed it to be warm and to have a good pulse in the posterior tibial, the dorsalis pedis, popliteal and femoral vessels. The effect of the operation was dramatic, not only in increasing the temperature of the leg immediately but also in relieving the vasospasm. The cyanosis disappeared rapidly and

the general condition of the patient began to improve remarkably. The anxiety and apprehension disappeared, and the pulse and blood pressure began to improve. The blood pressure remained at approximately 110 to 120 mm. Hg during the operation, and within a few hours had returned to a normal level.

Postoperatively a Levin tube was employed and the patient had some feeling of abdominal pressure and slight nausea. Otherwise, there were no complaints. The Levin tube was removed at the end of the second day and he was allowed to have liquids, which nauseated him for twenty-four hours. Following this, he was given a low residue diet and had normal passage of gas and stool within five days. He was kept in bed for thirteen days, and then allowed up with elastic bandages applied to both lower extremities. During this time he had been treated with anticoagulants.

There has been an adequate follow-up for one year, with evidence of good results.

COMMENTS

After realizing the pathological physiology which is present, one cannot fail to conclude that early recognition and treatment will save leg or life. The arteriospasm may be of varying degree and may be of short duration, in which case it will look like an ordinary thrombophlebitis. In the past we have more or less recorded those cases which have progressed to gangrene. Careful recordings of those good results obtained by therapy within the first eight hours will be contributory to better care of future cases. If an arterial embolus is best attacked before eight to ten hours have elapsed, it is natural to assume that release of this type of occlusion due to vasospasm will do the most good if it is done within eight to ten hours. In most recorded cases in which surgery was performed after this length of time, the thrombus was found to extend up to or beyond the renal veins and was found to be both a white and red thrombus.

One cannot advocate ligation of the inferior vena cava for any condition without studying the immediate and late results of such a procedure. In most patients whose lives are threatened by a potential pulmonary embolus, treatment may be satisfactory with superficial femoral vein ligation or with anticoagulants. There remains, however, a limited group of patients for whom ligation of the inferior vena cava is the procedure of choice. Some indications for this live-saving procedure are: embolism despite femoral vein ligation, spread of the thrombosis to both femoral and iliac veins, failure of anticoagulant therapy to control the spread of the process, sensitivity to dicumarol, advanced thrombosis before the patient is seen, lesions such as peptic ulcer or tuberculosis where hemorrhage may occur with anticoagulants, septic pelvic thrombophlebitis and phlegmasia cerulea dolens.

Some authors state that ligation of the inferior vena cava is not a procedure of election because of the late development of undesirable sequelae. Shea and Robertson [*16*] reported that of twenty-five patients who had ligation four or more years previously, only sixteen returned to full activity and the majority had impaired circulation of the extremities. Bowers and Leb [*1*] followed up thirty-three patients whose cavae were ligated one to seven years before demonstrating changes which contraindicated such routine use of the procedure.

Unless thrombosis extends up to or above the renal veins, the cava may be ligated in continuity inasmuch as a mechanical block is all that is considered necessary to prevent pulmonary embolism. The effect of the ligation should be just as good, from the vasospastic release, whether the cava is tied or severed. According to Madden [*8*], ligation is preferable to division because of the technical difficulty of the operation due to the collateral supply and also due to the definite intolerance of blood loss from the circulation at this site.

SUMMARY

1. The patient with phlegmasia cerulea dolens is offered satisfactory recovery through early operative therapy and blood replacement.

2. Vena cava ligation in continuity, with lumbar sympathectomy and postoperative anticoagulants is recommended as a satisfactory method of therapy for phlegmasia cerulea dolens.

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The Use of Adenylic Acid Suppositories in Subacute Thrombophlebitis and Varicose Ulcers

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THE use of adenosine-5-monophosphate* therapy in cases of pruritus and the complications of varicose veins was first described by Rottino et al. [1] in 1950, following its use in patients with Hodgkin's and other diseases. The drug provided a marked relief from itching and decrease in the inflammatory process associated with thrombophlebitis, and a rapid clearing up of varicose ulcers during the course of treatment. As a result of this work, Lawrence et al. [2], Pratt [3], Quintero [4], and Boller and co-workers [5] successively reported upon the use of muscle adenylic acid in these conditions. The adenylic acid preparation used in these studies was My-B-Den® Sustained Action† a preparation containing A5MP in a gelatin base for prolonged action upon intramuscular injection.

For the past six years I have continued to use My-B-Den as one of the primary methods of treating thrombophlebitis and the complications of varicose veins. This therapy has been so successful that it is believed this drug should be considered an integral part of the therapy of these diseases. However, the use of frequent intramuscular injections presents a number of difficulties. Patients must be seen daily or every other day over a prolonged period of time, which is inconvenient to them unless they are hospitalized. Furthermore, intramuscular therapy entails the pain inherent with any intramuscular injection plus the expense involved. The development of an adenylic acid suppository to supplement parenteral therapy was welcomed.

This report deals with the results of therapy using suppositories of muscle adenylic acid, each suppository containing 100 mg. of adenosine-5-monophosphate.* The suppositories were evaluated in fifty-one patients. There were twenty-three cases of subacute thrombophlebitis and twenty-eight cases of varicose ulcers.

In patients with varicose veins, the use of My-B-Den was limited solely to the treatment of the various complications, namely, acute, subacute and chronic thrombophlebitis, varicose eczema, stasis cellulitis, epidermitis and varicose ulcers. Varicose veins, *per se*, without the presence of any of these complications, do not constitute an indication for this type of treatment. The objectives of the evaluation were to determine (1) any sensitivity or irritating effects of the suppository itself, (2) any objection on the part of the patient to the use of suppositories and (3) the efficacy of treatment as compared to parenteral adenylic acid therapy.

METHOD OF EVALUATION

The same procedure was followed with each patient. On the initial visit of the patient, after diagnosis had been ascertained, an intramuscular injection of 100 mg. (1 cc.) of My-B-Den Sustained Action was administered to expedite the therapeutic response. Familiarity with the drug for many years has shown that favorable responses seldom can be obtained with a single injection. Hence, it was believed that the initial intramuscular injection would not confuse the

* Adenosine-5-monophosphate (A5MP) is also known as muscle adenylic acid.

† My-B-Den and My-B-Den Sustained Action are products of the Ames Company, Inc., Elkhart, Indiana.

* The adenosine-5-monophosphate suppositories used in this study were furnished by Dr. Norman L. Heminway, Medical Director, Ames Company, Inc.

evaluation of the suppositories. The patient was then instructed to insert one suppository rectally each night before going to bed. Each patient was next seen seven days after the initial visit and complete progress notes and physical observations were made. The patient was seen again one week later and questioned and examined similarly. If necessary, the drug was continued for the third week or longer.

RESULTS

Venous Thrombosis. At the end of one week the inflammatory processes in all patients with venous thrombosis were observed to be markedly improved, especially the local tissue edema. In one patient receiving My-B-Den for acute superficial thrombophlebitis of one leg, an extensive, rapidly spreading acute thrombophlebitis developed in the opposite leg which had enormous varicosities. The course of the thrombophlebitis, however, was short-lived and I believe this might have been due to the continued use of the drug.

Varicose Ulcers. In all but one of the patients with varicose ulcers there was a prompt decrease in the inflammatory reaction of the surrounding area, and a decrease in the size of the ulcer with loss of some of its indolent characteristics. Débridement of the ulcer with removal of the necrotic base usually was possible at the end of one week's therapy with My-B-Den suppositories.

Pruritus. The use of the suppository of muscle adenylic acid in pruritus was limited only to the itching associated with stasis dermatitis or varicose eczema and varicose ulcers. There were no cases in which it was used for generalized pruritus associated with other diseases. The suppositories produced a definite decrease in the itching associated with the complications of varicose veins. Forty-eight to seventy-two hours after therapy was initiated all patients without exception remarked about the local relief that was experienced. This undoubtedly was due to the decrease in the inflammatory reaction corrected by the use of the drug. Admittedly, the initial administration of My-B-Den intramuscularly helped to achieve this response, but it is considered very unlikely that the single intramuscular injection alone would have resulted in a 100 per cent relief of pruritus.

Inflammation. In every case there was a remarkable decrease, within one week, in the inflammatory reaction associated with superficial thrombophlebitis and stasis dermatitis due to varicose veins. These patients were seen after one week of therapy, at which time the area of redness had changed to a brownish discoloration and the active inflammatory process was markedly diminished in size. Where the inflammatory reaction had not disappeared completely in one week, patients were kept on the medication for another week, at the end of which time the inflammatory reaction had completely disappeared in each instance.

Edema. The effects of muscle adenylic acid administered intramuscularly in reducing local tissue edema have been described in previous publications [*1–5*]. A5MP administered rectally by suppositories was found to provide similar benefits in the patients observed in this investigation.

Pain. The relief of pain associated with subacute thrombophlebitis is closely associated with the relief of the inflammatory process. However, it is true that while there was a marked decrease in the pain and tenderness, there was not complete relief of pain because of the pathological changes which had taken place in the subcutaneous tissues, namely, fibrosis and thickening with compression of periosteum and adjacent structures. However, the pain and tenderness associated with the acute inflammatory process was decreased markedly.

Stasis Dermatitis (Varicose Eczema). The eczema associated with stasis dermatitis due to the post-thrombotic syndrome and varicose veins is promptly relieved by the rectal administration of My-B-Den. There was a decrease of the scaling, oozing and edema in the inflammatory reaction associated with this complication. As described previously, with My-B-Den administered intramuscularly, the skin becomes softer, smoother and loses its scaly and oozing characteristics. There was not one instance of failure to accomplish these effects in the patients treated with the suppositories.

Side Actions. In not one case was there any evidence of rectal, anal or perianal irritation or sensitivity as manifested by either rash, itching or burning. In a few instances there were some increased bowel movements, probably due to the mechanical stimulation of the suppository, but this disappeared after the first few days of treatment.

CASE REPORTS

CASE I. C. D., a fifty-one year old woman, was seen on September 10, 1956, with an ulcer above the left internal malleolus which had been open for one week. She had had an ulcer at the same site one year previously which took several months to close. She had had superficial thrombophlebitis of the left leg in 1929 and had undergone bilateral ligation in 1951 which did not relieve her varicosities. Her ankles were swollen at the end of each day but were relieved by bedrest. She did not wear any elastic support. Examination revealed large venous sinuses on the inner aspect of the left lower leg with marked increase in venous pressure from the perforating veins. On the left inner aspect of the ankle there was an extensive area of varicose eczema with a necrotic ulcer surrounded by an area of subacute inflammatory epidermitis and a wider area of stasis dermatitis, and cellulitis. An intramuscular injection of 100 mg. of My-B-Den Sustained Action was given and she was started on a regimen of one 100 mg. suppository of A5MP rectally each night. The ulcer was débrided and covered with sterile dressings and an elastic bandage. She was seen one week later and reported that her leg felt very much improved and the inflammatory reaction and burning had markedly decreased. There was still some itching of the skin locally but the ulcer had markedly decreased in size and was no longer painful. No adverse reactions to the suppositories were experienced or observed. A fresh sterile dressing was applied and she was continued on the same regimen of My-B-Den suppositories. Seen again one week later, she stated that she was free from all symptoms. On examination, all signs of the inflammatory reaction were gone. The epidermitis and eczema had disappeared, although the skin was still somewhat discolored a reddish brown. The ulcer had healed completely within the two weeks of therapy. The suppositories, consequently, were discontinued and the patient advised to have a ligation and stripping operation to correct the venous insufficiency of the left leg.

CASE II. B. C., a fifty-one year old man, had a history of varicose ulcers of both legs which were opened six months previously after having been treated by injections of sclerosing agents several years previously. The patient now complained of a burning sensation in these areas which showed no evidence of healing. Examination revealed varicose veins of both legs with edema and a patch of varicose eczema 4 to 5 inches in diameter on the inner right ankle and outer left ankle. There was evidence of pigmentation due to stasis dermatitis in both legs, and there was an ulceration with a necrotic base about 1 cm. in diameter on the left leg and 1 to ½ cm. on the right leg. There was no arterial insufficiency as all pulsations were normal. My-B-Den Sustained Action, 100 mg., was administered intramuscularly and My-B-Den suppositories, 100 mg., were prescribed to be taken nightly. Moist dressings to be changed three times daily to help débride the necrotic ulcers were also recommended. The patient was seen five days later because of considerable oozing from the eczematous areas. At this time, however, there was marked improvement of both areas as the inflammatory processes had decreased markedly and the burning sensations had disappeared. The ulcer on the right leg had closed completely and the ulcer on the left leg remained only as a very small opening. The ulcer on the left was covered with a sterile dressing and compression bandage. The same regimen of suppositories was continued. The patient was seen again four days later at which time the left ulcer also had completely healed. At this time the inflammatory process and eczema were observed to have disappeared. The pigmentation, however, remained. No local or systemic ill effect from the use of the suppositories was noted. Medication was discontinued and the patient was instructed to continue wearing the compression bandages.

COMMENTS

There were two types of venous defects in the patients observed in this study. The first type was one in which there were large varicosities with evidence of insufficiency of the venous system above the area of involvement. In these cases My-B-Den suppositories were used in conjunction with mechanical compression such as the use of sponges, rubber and elastic bandages. It must be mentioned, however, that these patients had been using these adjuncts, particularly compression bandages, previous to initiating adenylic acid therapy, but did not obtain appreciable beneficial effects with them alone.

The second type of venous defect was one in which there was no apparent venous insufficiency above the areas involved. In these cases the pathology was due to incompetence of the deep or communicating veins, and no superficial vein that could be ligated or obliterated was discernible. Compression bandages had also been used with these cases previously without effective results. It was in this second type of case that the most remarkable improvement occurred with My-B-Den therapy.

An important point to remember is that all of these patients become ambulatory with the relief of their inflammatory processes. In not one case was there any objection on the part of the patient to the use of the rectal route of

administration. As a matter of fact, this type of administration was welcomed in preference to frequent intramuscular injections.

CONCLUSIONS

1. The effects of suppositories containing 100 mg. of adenosine-5-monophosphate were evaluated in fifty-one patients with varicose ulcers and subacute thrombophlebitis. Marked improvement was noted in all cases. Most patients experienced beneficial effects within forty-eight to seventy-two hours after first using the suppositories. No irritation or significant side effects were attributable to the use of the suppositories or objections made to this form of medication.

2. My-B-Den suppositories provide an effective means of administering adenosine-5-monophosphate, a drug which should be considered an integral part of the therapy of the complications of varicose veins and thrombophlebitis.

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Effect of Vitamin A, Niacin and Riboflavin on Vascular Lesions

A PRELIMINARY REPORT

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CERTAIN specific changes in blood vessel metabolism in animals have been observed when three nutritional factors are given in very large doses. This is a suggested application in the treatment of peripheral vascular diseases, particularly when associated with smoking. The carbon monoxide in tobacco smoke [1] combines with hemoglobin to form carboxyhemoglobin and checks its oxidizing function. The production of new red blood cells is stimulated and is reflected in elevated packed red blood cell volumes, as shown by Eisen and Hammond [2] who indicated that this "thickening" of the blood could contribute to its thrombosing. Accelerated clotting time following smoking is reported in Table 1 of this study and is further evidence that smoking may influence thrombus formation.

Therapy consists of vitamin A, niacin (nicotinic acid) and riboflavin and has been applied to patients for periods ranging from one to ten years. The subjects were private patients selected for their willingness to cooperate and because they were easy to follow up. Benefit depends on the specific action of the vitamins on blood coagulation, composition and blood vessel wall and, in the case of niacin, on the collateral circulation.

There is experimental evidence that large doses of vitamin A can retard clotting. Two factors in the mechanism of blood coagulation, calcium and prothombin, are known to be affected. Large doses of vitamin A have produced an excess of calcium excretion over intake [3] and, although synthesis of vitamin K is not impaired, it has caused a marked hypothrombinemia with hemorrhages, associated with a lowering of the packed red blood cell volume (hematocrit) [4,5] and naturally a "thinning" of the blood.

Furthermore, vitamin A may favorably influence blood vessel walls of patients by affecting surface tension. The actual improvement in experimental atheromatosed vessels has been attributed to vitamin A's high surface tension acting directly on the hydrophilic surfaces of the vessel wall [6]. Moreover, large doses of vitamin A have been shown to suppress the "thick," keratinizing epithelial process and to substitute a "thin," mucous-secreting epithelium [7]. Therefore, the improvement in patients may be a direct result of vitamin A's action on the thickened endothelium of the arteriosclerotic blood vessel. There may be actual decalcification of the calcified vessels. This effect of vitamin A in large doses has been shown to take place in bony structures of animals [3].

It is also recognized that niacin exerts a vasodilator action on blood vessels [8], aids angiospasm in retinal hypertension [9], and reinforces the action of acetylcholine [10], a vasodilator itself [11]. It has lessened scar in man following corneal ulcers [12]. Its deficiency is not known to selectively damage the heart; yet a very high incidence of abnormal electrocardiograms is reported in human pellagra [13]. They are myocardial defects and most of them disappear promptly following niacin therapy [13]. Its effective use in treating cardiovascular failure and the embolic syndromes of the limbs has been reported [14].

Since smoking lowers oxygen supply [2], the animal studies showing that niacin [15] and riboflavin [8] can compensate in anoxia (low oxygen pressure) also apply to treatment of

smokers. A minute amount of riboflavin in the perfusion medium restored normal muscular contractions to the heart weakened by low oxygen [8].

There is a functional interrelationship among the three vitamins of our therapy. Niacin and riboflavin are both "respiratory" enzymes [16,17,19]. Niacin has been shown to be essential in vitamin A's metabolism [20–22]. Riboflavin [23–27] and vitamin A[6] have prevented or corrected faulty fat metabolism which is abnormal in the atherosclerotic type of arteriosclerotic blood vessels.

METHOD

On the basis of the evidence presented herein and in my previous studies [2,28] indicating the need to alter the blood composition of smokers, clinical tests were conducted. The private patients selected for study included thirteen cases of arteriosclerotic peripheral vascular disease, two cases of arteriosclerotic heart disease and two cases of thromboangiitis obliterans. All were heavy cigarette smokers; except one complete abstainer. (All were on normal diets.)

Laboratory tests of clotting time (Lee and White) [31], blood sedimentation (Westergren) [32] and oscillometric readings as well as x-ray photographs of the lower extremities were made. Non-smoking controls of clotting time and blood sedimentation were performed on seventy-five persons, including the seventeen subjects who had abstained from smoking for one month. Investigation included blood cholesterol levels, hematocrit, hemoglobin, counts of red and white cells and of platelets, urinary calcium and vitamin A assays.

Medication initially consisted of placebos given for three to six weeks. The patients were ordered to stop smoking entirely.

At the end of this period, the new therapy was begun. Its potency was 50,000 U.S.P. units of vitamin A palmitate, 50 mg. niacin (nicotinic acid) and 5 mg. of riboflavin. This dose* was administered daily after each meal and at bedtime for three to six months. The term, *ANR*, will be used in the rest of this paper to denote this formula.

For clarity, clinical data from this study are presented partly in tabular form. Table 1 shows the effects of cigarette smoking on clotting time and blood sedimentation in four patients. Two of the histories are given in detail. They are typical of the group of seventeen patients. However, the case histories give only a sampling of the repeated blood and oscillometric determinations made in all seventeen cases, which convinced us that our results with ANR were based on firm objective evidence and that the therapy was really effective.

RESULTS

The initial examination, when the patients were smoking, showed acceleration of clotting time, decrease of blood sedimentation rate, elevation of hematocrit (packed red blood cell volume) and increase of hemoglobin and red blood cells—all confirming the earlier findings of "thickened" blood [2]. In some cases there was an elevation of blood cholesterol levels. Physical examinations revealed faint or absent pulsations in the lower extremities with low or absent oscillometric readings.

Complete abstinence from smoking for one to seven days or longer caused a greatly reduced hematologic response: the clotting time was prolonged; blood sedimentation rate increased; hematocrit, red counts and hemoglobin reduced and, if the blood cholesterol had been elevated, it was diminished.

To test the immediate effect of cigarette smoking after one to six weeks' abstinence, the patients were given three or four cigarettes to smoke and inhale in succession. Tests of clotting time and blood sedimentation made immediately before and after smoking showed that clotting time was cut in half and was below the normal of five to eight minutes for the test; and the blood sedimentation rate was reduced. In the patient with thromboangiitis obliterans, the oscillometric readings were rapidly and greatly diminished. These findings confirmed our earlier impression of "thicker," more rapidly clotting blood in smokers [2]. (Table 1.)

Management of the patients was as follows: complete abstinence from smoking was ordered along with placebos plus aspirin or codeine for relief of pain for three to six weeks. This regimen was without benefit. All continued to complain of early intermittent claudication in their

* For convenience, the vitamin A, niacin and riboflavin formula was incorporated into a single, solid-core capsule of gelatin emulsion [29,30] which disintegrates very gradually and thus prolongs the effectiveness of the vitamins. This capsule, "provasin," was supplied for our study through the courtesy of Gordon Pharmaceuticals, New York, N. Y.

TABLE I

THE EFFECT OF CIGARETTE SMOKING ON CLOTTING TIME, SEDIMENTATION RATE AND OSCILLOMETRIC READINGS OF THE LOWER EXTREMITIES AFTER ABSTINENCE FROM SMOKING FOR AT LEAST ONE MONTH

Data	Clotting Time [31] (Lee-White)	Sedimentation Rate [32] (Westergren)	Oscillometric Readings
CASE I, a 47 year old white female with APVD and AHD; smoked 1½ packs daily; smoked 25 years	*Not smoking:* 4 min. 32 sec. *After 3 cigarettes:* 2 min. 18 sec.	*Not smoking:* 23 mm. in 1 hr. *After 3 cigarettes:* 17 mm. in 1 hr.	*Not smoking:* Left ankle, 1.0 Left calf 2.0 *After 3 cigarettes:* Left ankle, .75 Left calf, 1.00
Case II,* a 44 year old white female with TAO; smoked 1½ to 2 packs daily; smoked 30 years	*Not smoking:* 4 min. 13 sec. *After 4 cigarettes:* 2 min. 18 sec.	*Not smoking:* 28 mm. in 1 hr. *After 4 cigarettes:* 20 mm. in 1 hr.	*Not smoking:* Left ankle, 1.50 Left calf, 2.00 *After 4 cigarettes:* Left ankle, 0.25 Left calf, 0.50
Case III, a 41 year old white male with TAO; smoked 2½ to 3 packs daily plus 3 to 5 large cigars; in 1943, 1944 and 1945, smoked 6 packs daily	*Not smoking:* 4 min. 20 sec. *After 3 cigarettes:* 2 min. 15 sec.	*Not smoking:* 19 mm. in 1 hr. *After 3 cigarettes:* 14 mm. in 1 hr.	*Not smoking:* Right ankle, 1.50 Right calf, 2.0 *After 3 cigarettes:* Right ankle, .50 Right calf, 1.00
Case IV, a 46 year old white male with APVD; smoked 1½ to 2 packs daily	*Not smoking:* 4 min. 21 sec. *After 3 cigarettes:* 2 min. 20 sec.	*Not smoking:* 15 mm. in 1 hr. *After 3 cigarettes:* 10 mm. in 1 hr.	*Not smoking:* Right ankle, 1.0 Right calf, 1.50 *After 3 cigarettes:* Right ankle, .50 Right calf, 1.00

NOTE: Normal clotting time for this test: 5 to 8 minutes.
APVD—arteriosclerotic peripheral vascular disease.
AHD—arteriosclerotic heart disease.
TAO—thromboangiitis obliterans.
* This patient showed the marked and immediate effect of smoking on the arterial pulse.

lower extremities and of substernal distress. There was no change in the objective findings.

Based upon the action of vitamin A in delaying clotting time, its effects on calcium excretion and thickened and/or atheromatosed lining tissues in animals; niacin's vasodilator activity; and the protection niacin and riboflavin have afforded in experimental anoxia (low oxygen), the vitamin A-niacin-riboflavin (ANR) formula described above was given after each meal and at bedtime for three to six months. When improvement warranted, the dose was reduced—in some patients to as low as one capsule daily.

Improvement on ANR therapy occurred within two to four weeks in fourteen of the seventeen patients. Palpable pulses, increased oscillometric figures and higher skin temperatures paralleled the subjective signs of improvement which were diminished leg pain and cramps, increased walking capacity and relief of substernal distress. When the ANR treatment was discontinued for a few days, symptoms of intermittent claudication and substernal distress returned quickly (within forty-eight to seventy-two hours), although the patients had completely abstained from smoking.

Because many patients cannot break the tobacco habit, the subjects were allowed to smoke, to find out whether or not the ANR formula could protect against the effects of cigarette smoking. When ANR was discontinued, the symptoms returned within forty-eight hours. However, when smoking was per-

mitted and ANR therapy continued, the patients felt as much improved as when they were not smoking but on ANR. Moreover, objective signs confirmed this improvement. (Cases I and II and Table II.)

TABLE II

THE EFFECT OF HIGH VITAMIN A-NIACIN-RIBOFLAVIN (ANR FORMULA) ON HEMOGLOBIN AND HEMATOCRIT WHILE THE PATIENT IS SMOKING (CASE 18, MR. H. R.)

Date	Hematocrit [34] (Packed red blood cells)	Hemoglobin (gm. %)	Medication
3/4/57	56	16	First visit, no medication; ANR 4 times daily ordered
4/29/57	53	15	On ANR 4 times daily since 3/4/57
5/4/57	47	13.5	On ANR 4 times daily for two months

NOTE: In spite of smoking, both hematocrit and hemoglobin are reduced. This suggests that ANR has protected the patient from the usual thickening of blood in smokers.

CASE 1. Mrs. G. M., a forty-seven year old white woman was seen on August 15, 1956, complaining of substernal distress on exertion and constant pain in both legs on walking and at rest. The condition had persisted for ten years, and had become progressively worse in the past two years on walking only ten to twenty steps. The patient smoked one and one-half to two packs of cigarettes daily for the past twenty-five years.

Physical examination revealed heart sounds to be regular in rate, rhythm and force; there were no murmurs, and blood pressure was 130/90 mm. Hg. Lower extremities revealed no pulsations except greatly diminished femoral arteries and on auscultation there were systolic murmurs over the left femoral and iliac arteries. Oscillometric readings at both ankles were faint. Right and left calves were 0.75. X-rays showed calcification of the arteries of the lower extremities. The hematocrit was 40 per cent; the blood cholesterol was 362. The condition was diagnosed as arteriosclerotic peripheral vascular and arteriosclerotic heart disease. Placebos and sedation for pain were given for a week without relief.

On August 23rd large doses of vitamin A, niacin and riboflavin were administered four times daily and the patient was advised to stop smoking at once. On September 5, 1956, pulses were not palpable in both lower extremities, the oscillometric readings were right and left ankle, 0.75; right and left calves, 1.0. Pains greatly diminished and the patient was able to walk one to two blocks without pain. The hematocrit was 35 per cent and blood cholesterol was 285.

On October 5, 1956, pulses were barely palpable in both feet, oscillometric readings were right and left ankle, 1.0; right and left calves, 1.25. The patient was able to walk five to six blocks without pain. The hematocrit was 34 per cent and blood cholesterol was 265.

On November 25, 1956, pulses were palpable in both lower extremities. The oscillometric readings were left ankle, 1.50; right ankle, 1.75; left calf, 2.0; and right calf, 2.0. The patient felt no pain on walking twenty blocks. Therapy was continued. After three months of therapy the patient admitted that she had been smoking continuously; in spite of this she continued to improve subjectively and objectively as long as she continued the ANR therapy. However, when she discontinued medication severe pains in her legs returned and she was unable to walk. When she resumed therapy her leg pains subsided and walking capacity improved.

CASE 2. Mr. I. G., a fifty-six year old white man was first seen in 1949 complaining of pain in both calves on walking one-half to one block. This pain was relieved by rest. The patient smoked one and a half to two packs of cigarettes daily. Duration of this condition at this time was three years. Physical examination revealed no palpable pulses in either foot except diminished popliteals and femorals. Oscillometric readings were right and left ankle, 0.5; right and left calves, 0.75. X-rays revealed calcification of arteries in the lower extremities. The hematocrit was 56 per cent; the red blood cell count was 7,000,000 per cu. mm. and hemoglobin was 17 gm. per cent. The blood cholesterol was 375. The diagnosis was arteriosclerotic peripheral vascular disease. Therapy at this time consisted of kiophyllin® and phenobarbital with cessation of smoking. The patient did not present himself again until July 1954 at which time he was in considerable distress on walking a few steps. Examination revealed no pulses palpable in both lower extremities except femorals. The oscillometric readings were right and left ankles, 0.0; right and left calves, 0.5; hematocrit, 58 per cent and hemoglobin 17 gm. per cent. The patient was now given large doses of vitamin A, niacin and riboflavin four times daily. Within one month the leg pains were considerably less and the patient's walking capacity improved.

In September 1954, the oscillometric readings were right and left ankles, 0.5; right and left calves, 0.75. The patient's walking capacity had increased to two blocks without pain. The pulses were not palpable.

In November 1954, foot pulses were palpable; the oscillometric readings were right and left ankles, 1.0; right and left calves, 1.25. The patient's walking capacity was six blocks without pain.

In December 1955, the oscillometric readings were right ankle, 1.0; right calf, 2.0; left ankle,

1.25; left calf, 2.0. The patient had no difficulty in walking. He had been receiving ANR therapy for sixteen months.

In December 1956, the pulses were palpable in both legs. The oscillometric readings were right ankle, 1.50; right calf, 2.75; left ankle, 1.75; left calf, 2.75. The patient was able to walk one mile on level ground without pain. He claimed that he had not been smoking since therapy began.

When last seen in August 1957, the patient had resumed smoking in November 1956 but had continued with ANR therapy. His subjective and objective improvement had continued.

ANR therapy has proved useful in hardening of the arteries, uncomplicated by smoking. One patient with arteriosclerotic heart disease survived four attacks of coronary thrombosis infarction in the past ten years. He has never smoked, has been receiving large doses of vitamin A (150,000 U.S.P. units daily) for the entire ten years, and is able to be active in business. On the basis of our findings, we conclude that the high vitamin regimen has contributed to his survival and ability to carry on normally.

It is recognized that in occasional patients toxicity to large doses of vitamin A may develop. Signs of poor tolerance are anorexia, headache, increased fragility of the finger nails and rarefaction of the bones. A dose of 50,000 U.S.P. units is considered non-toxic for any adult. Tests over periods of several months have shown that most persons tolerate 150,000 to 250,000 U.S.P. units of vitamin A daily very well. The patients in our study were watched carefully. Urinary calcium and vitamin A assays during ANR treatment were within normal range in our patients with the exception of a patient who had been receiving 150,000 U.S.P. units daily for twelve years. He showed a slight excess of urinary calcium. No other signs were observed except in the patients who had calcified areas in the leg arteries. After six months of ANR therapy, their x-rays revealed slightly diminished opacity in these areas—perhaps a true decalcification of the lesion, and obviously a result to be desired. Flushing due to niacin was transient, if observed at all. There is no reported toxicity to riboflavin [*19*].

SUMMARY AND CONCLUSIONS

A new potent combination of vitamin A, niacin and riboflavin (called the ANR formula) has been applied intensively for one to ten years in thirteen cases of arteriosclerotic peripheral vascular disease, two cases of arteriosclerotic heart disease and in two cases of thromboangiitis obliterans. Sixteen of these patients were heavy cigarette smokers and one was a non-smoker. All were on normal diets.

This study includes repeated determinations of blood clotting, sedimentation, red cell counts and packed cell volumes (hematocrit), hemoglobin, blood cholesterol, as well as urinary calciums, vitamin A assays and x-ray films of all patients' lower extremities before and during ANR treatment. Oscillometric readings were also made very frequently.

Recognizing how difficult it is to break the cigarette habit, I studied the effects of ANR therapy when the patients were smoking and when they were not. The use of the ANR formula in these patients is based upon the following:

(1) Tobacco smoke contains carbon monoxide which combines irreversibly with hemoglobin, checking its oxidizing power and thus stimulating production of new red cells.

(2) This study and a previous one have disclosed that cigarette smokers' blood is "thickened" [*2*] and clotting time reduced below normal. (Table 1.)

(3) High doses of vitamin A, niacin and riboflavin have retarded clotting, "thinned" the blood, improved lesions in lining tissues, dilated blood vessels and compensated for anoxia (low oxygen) in animals.

Therefore, the ANR formula (50,000 U.S.P. units vitamin A palmitate, 50 mg. niacin and 5 mg. riboflavin) was given to the patients. In fourteen of the seventeen cases there was improvement within two to four weeks. Subjective signs were relief of leg pain and cramps and of substernal distress with increased walking capacity. They paralleled the return of pulsations and increased oscillometric readings in the lower extremities. This improvement was marked after three to six months of ANR therapy and occurred whether the patients smoked or not.

Withdrawal of the ANR combination brought the prompt return of the initial syndrome of intermittent claudication and substernal distress, even when the patients were not smoking. Objective signs also returned. Placebos were without effect.

The findings with large doses of vitamin

A-niacin-riboflavin formula in these seventeen patients is presented as a preliminary report.

APPENDIX

EXPERIMENTAL METHODS

Lee and White's Venous Blood Method for Determining Coagulation Time [31]. (1) Rinse a sterile 10 ml. syringe fitted with a sterile 20 gauge needle with sterile saline solution. Rinse two absolutely clean test tubes, having an internal diameter of 8 mm. with a physiologic saline solution. (2) Conduct a venipuncture quickly and with a minimum of stasis withdraw about 4 ml. of blood. *Note the time.* Remove the needle from the syringe and immediately discharge about 1.5 ml. blood into each test tube. (3) If the room temperature is between 20° and 32°C., the tubes may be kept at room temperature; if not, stand the tubes in a glass of water at 20° to 25°C. (4) Wait three minutes and then tilt one of the tubes every half minute until the blood can no longer be disloged by tilting. Then begin tilting second tube at the same intervals until the blood no longer flows and the tube can be inverted. *Note the time.* (5) The time elapsing from the removal of blood is the coagulation time. Normally, it varies from five to eight minutes, averaging six and one-half minutes. If the test tube has an internal diameter of 9 mm., the normal coagulation time varies from six to eleven minutes.

Sedimentation Rate of Erythrocytes (Westergren Method) [32]. Apparatus required is a Westergren tube and rack. It is also convenient to use a tube with a mark indicating 5 cc. This may be a graduated centrifuge tube or a plain test tube with a mark etched on it at the 5 cc. level. The only reagent is a 3.8 per cent solution of sodium citrate.

Technic: (1) Transfer with a graduated pipette exactly 0.5 cc. of the 3.8 per cent solution of sodium citrate to a tube with the mark at 5 cc. level. (2) Withdraw 5 cc. of venous blood in a dry syringe and place 4.5 cc. of it in the tube containing the anticoagulant. The tube, now filled to the 5 cc. mark, is inverted two or three times to mix thoroughly the anticoagulant with the blood. (3) Fill a Westergren tube exactly to the 0 mark and place it in the rack. The bottom of the tube must be placed firmly against the rubber stopper in the base of the rack before removing the finger from the top of the tube. The tube must be held firmly by the clip at the top of the rack in an exactly vertical position. The rack is constructed to hold twelve or more tubes. (4) Read the fall of the corpuscles in millimeters in exactly sixty minutes. It may be of interest also to note the fall in thirty minutes.

With this method, the normal sedimentation rate for men's erythrocytes is 0 to 15 mm. in one hour. The rate for healthy women is 0 to 20 mm. in one hour.

Determination of the Packed Red Blood Cell Volume or Hematocrit [34]. Blood is withdrawn in the amount of 4.5 cc. from the median cubital vein and put into an oxalated tube containing dried powder of balanced amounts of sodium and potassium oxalate which has been over-treated. The oxalated blood is then thoroughly mixed slowly for two minutes and drawn into a capillary pipette, by means of which it is expelled into the hematocrit. As pressure is applied to the bulb and the blood slowly forced out, the pipette is withdrawn. This must be done at such a rate that bubbles of air will not form in the hematocrit tube. The hematocrit is filled exactly to the 0 mark at the left side of the scale and then centrifuged at 3,450 revolutions per minute for thirty minutes. The object of centrifugation is to secure complete packing of the corpuscles.

The volume of packed red cells may be read directly from the numbers on the right side of the scale. The reading of volume of packed red cells is made at the bottom of the meniscus of the deep red layer of red cells, adjacent to the reddish gray layer of packed leukocytes and platelets. All tests are to be performed immediately after drawing the blood. Special care must be taken to see that all syringes and needles are perfectly dry.

All hemoglobin determinations were made by the Leitz photometer method.

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Tumors of the Testicle in Childhood

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TUMORS of the testicle which occur during infancy and childhood constitute an intensely interesting group of neoplasms. The trigerminal potential of the testicular cells provides the basis for an intriguing array of growth patterns, each with a somewhat different architectural structure and each inherently capable of invasion and malignancy. Needless to say, such unpredictable characteristics emphasize the importance of early recognition and immediate therapy but the extreme infrequency with which tumors of the testes occur in children does not permit any great individual experience in their diagnosis and management. Kretschmer [*10*], for example, refers to a survey of the literature between 1803 and 1944 by Matassarin, who could find only 131 testicular tumors occurring in children under the age of fifteen during that period of time. A more recent report by Doyle [*6*] states that only twenty-five proved cases of embryonal carcinoma in children were found in the entire literature for a thirty-year period prior to 1955. The Canadian Tumor Registry has tabulated seven cases of adenocarcinoma of the testes in infants [*12*], and Rusche [*20*] compiled the records of twelve tumors, both benign and malignant, from hospital admissions covering a twenty-five-year period. Melicow [*14*], Boehme, Bagley and Pumphrey [*3*], Magner and Bryant [*11*], Meltzer and Bloom [*15*] and others [*2,5,22–25*] have also contributed case reports. Including the analysis of those patients as far back as 1803, however, it is unlikely that the total number of published reports of testicular neoplasms of infancy and childhood exceeds 160 cases.

The rarity of these tumors therefore warrants a continuation of the recording of observations and data relative to them. This thought has prompted us to discuss two cases of childhood testicular tumors which we have recently treated. One of these represents a malignant growth and the other a microscopically benign type of neoplasm.

CASE REPORTS

CASE 1. A. C. R., a forty month old white child, was seen on February 4, 1954, because of a swollen, somewhat tender left testicle which the mother had first noticed five days prior to the visit. No other symptoms were present. Physical examination was entirely negative with the exception of the left scrotal compartment which was occupied by an ovoid-shaped, smooth mass approximately 4 cm. in diameter. The result of examination by transillumination was questionable, and pressure failed to reduce the mass. The right testicle was normal. No inguinal glands were palpable. Past history was non-contributory; the child had been in good health except for an episode of transient jaundice in December, 1953.

The patient was admitted to General Hospital on February 10, 1954. X-ray examination of the chest revealed no abnormalities. Red blood cell count was 4,740,000 per cu. mm., white blood cell count 14,800 per cu. mm. and hemoglobin 13.4 gm. per cent. The sedimentation rate was 11 mm. per hour and the differential count was normal. Urinalysis was normal. Physical examination of the child was unchanged from that recorded on February 4th.

At surgery undertaken on February 11th a transverse scrotal incision was made and the testis delivered into the wound. It was observed to be completely replaced by a firm, greyish tumor mass. The entire organ and the distal 3 inches of the spermatic cord were removed. The patient was returned to his home on the following day and made an uneventful postoperative recovery.

Pathological examination revealed the following: Grossly, the specimen consisted of a

FIG. 1. Case I. Section taken from an embryonal carcinoma in a forty month old child. The characteristics of the cells reflect the malignant potential of this tumor. This child is alive and well, however, with no evidence of recurrence three years after the testicle was removed. Original magnification × 420.

FIG. 2. Case II. This testicle containing a teratoma was removed from a twenty-one month old child. Gross inspection of the mass revealed it to contain elements of bone, cartilage and mucus-secreting tissue.

testicle measuring approximately 3.5 by 3.0 cm. along with approximately 5 cm. of vas deferens. The external surface of the organ was smooth, grey and relatively glistening, although there appeared to be some increased vascular prominence. The sectioned surface of the testis had a firm, greyish yellow appearance which showed focal areas of hemorrhage and multiple small cystic spaces measuring up to 3 mm. in diameter. The parenchyma of the testis bulged from beneath the capsule on sectioned surface.

Microscopically, three sections of the testis revealed one focal area of recognizable, relatively unaltered architecture. Otherwise there was replacement of the testis by a poorly differentiated malignant neoplasm that varied in appearance from a solid cellular arrangement to a more adenomatous pattern with irregular-sized spaces partially filled with a pink-staining proteinaceous material. The stroma was rather loose and in some fields there was the suggestion of small clusters of fat cells. The neoplastic cells were of large size and poorly defined. The nuclei were large, irregular and contained one or more large, dark-staining nucleoli. Mitotic activity, in many instances atypical, was excessive. There appeared to be invasion of the testicular capsule but there was no definite evidence of local spread beyond the confines of the testis proper. The epididymis and the vas deferens showed no significant microscopic alteration. The diagnosis was embryonal carcinoma of the testicle. (Fig. 1.)

This child did not receive postoperative

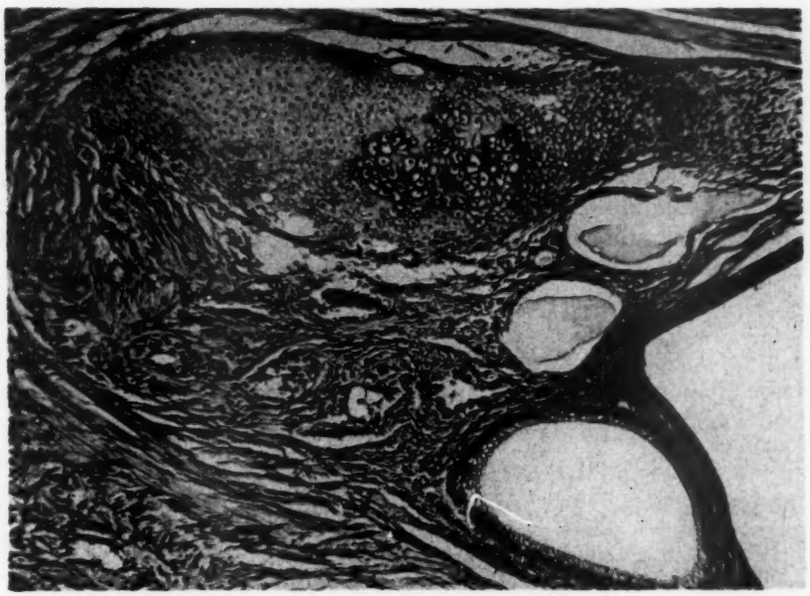

FIG. 3. Case II. Section taken from a teratoma of the testicle in a twenty-one month old child. The tumor contains bone, bone marrow, hyaline cartilage, bronchial epithelium and glands, stratified squamous epithelium, sympathetic ganglia, smooth muscle and elastic tissue. All the elements are benign. Original magnification × 130.

radiation therapy but has been followed up carefully for the past three years. No evidence of recurrence or spread of the tumor has been detected to date.

CASE II. D. J. W., a twenty-one month old white infant, was seen on January 21, 1957, because of an acute upper respiratory infection. Physical examination revealed acute tracheobronchitis and also a very firm, symmetrically enlarged left testicle approximately 3 cm. in diameter, which failed to transilluminate. The child's mother stated that this mass had been present for about one month without change in size and was first noticed following a bruise to the scrotum. There was no evidence of inguinal adenopathy and the spermatic cord was normal. The right testicle did not appear to be diseased.

A No. 20 needle was placed into the mass, but neither blood nor fluid was obtained. The patient was therefore given antibiotic therapy for the upper respiratory infection and scheduled for surgery.

The child was admitted to General Hospital on January 26th. X-ray examination of the chest was normal. Red blood cell count was 3,820,000 per cu. mm. and the white blood cell count 11,600 per cu. mm., with a normal differential. The hemoglobin was 10.1 gm. per cent. Urinalysis was negative. Temperature taken on admission was 99.0°F. rectally, and the physical examination was normal with the exception of the enlarged left testicle as noted at the previous visit.

At surgery performed on January 27th a left scrotal incision was made and the testicle and spermatic cord were delivered into the wound. Gross examination revealed diffuse enlargement of the organ but no evidence of spread beyond its confines. Prior to removal, the testicle was incised and was found to be entirely replaced by a mass consisting of loculated areas of cartilaginous structures, calcium deposits, sebaceous material and mucus. Complete orchiectomy with high ligation of the cord was performed. The child was returned to his home on the day following surgery and has made an uneventful postoperative recovery.

Pathological examination revealed the following: grossly, the specimen consisted of an ovoid testicular mass measuring 2.5 by 2 by 1.6 cm. Dissection revealed a somewhat nodular, yellow-gray to pink tissue. A distinctly mucoid material protruded from some cut surfaces and actual cysts were present. Other greenish black foci of semi-liquid mate-

rial were seen. On attempted incision some very hard material such as bone or calcium appeared to be present. (Fig. 2.)

Microscopically, sections showed a variety of types of tissue. Clearly seen were bone, bone marrow, hyaline cartilage, bronchial epithelium and gland, stratified squamous epithelium, sympathetic ganglia, smooth muscle and elastic tissue. All these elements were quite well differentiated and none of the tissue appeared malignant. The diagnosis was teratoma of the left testis. (Fig. 3.)

This child was not given x-ray therapy, and to this date no evidence of spread or recurrence of the tumor has been noted.

COMMENTS

Tumors of the testicle have been classified in several ways by a number of writers [*1,4,9*]. Friedman and Moore [*7*] were the first to suggest a simplified means of categorizing teratoid tumors based upon their study of 200 intrascrotal neoplasms from the Army Institute of Pathology. Four basic types were demonstrated, namely, (1) the adult or mature teratoma, (2) the seminoma, (3) the embryonal carcinoma, and (4) the chorionic carcinoma. Because of their close relationship the last two groups may well be consolidated under the term trophoblastoma. Other authorities such as Willis [*27*] would prefer that the term embryonal carcinoma be abandoned and the tumors regarded as poorly differentiated malignant teratomas. Magner and his co-workers [*12*] have described an unusual class of infantile teratoid tumors to which they have given the name adenocarcinoma with clear cells. The close relationship of testicular tumors to other adenomatoid tumors of the genital sphere has been pointed out [*8,21*] and the resemblance of the tumors to neoplastic formations occasionally discovered in myomas of the uterus and in the ovary has been noted [*18*].

While the exact etiology of testicular tumors is unknown, most authors agree that the teratoid neoplasm represents an abnormal result of cellular growth which is attempting to reach formation of the embryo. Moore [*17*] has postulated the theory of parthenogenetic origin. Magner et al. [*12*] have used the term dysontogenetic. Based upon the simple premise that unknown factors or agents exert their influence upon the totipotent cells of the testes, Melicow [*14*] has presented an excellent outline of the natural history as well as a working classification of the disease. His opinion is that most testicular tumors arise from the component cells of the organ. These are either (1) the spermatazoa and their derivatives or (2) the interstitial or Sertoli cells. The former give rise to the germinal tumors, while the latter are the origin of the non-germinal growths.

The family of germinal tumors is subdivided into two subgroups depending on differences in the original cellular response to the unknown factors previously mentioned. When the cells are stimulated to divide and multiply but still retain their trigerminal potential and maintain the original appearance, the resulting tumor is a unicellular mass known as a seminoma. If the carcinogenic factor not only stimulates the cells to divide but also forces them to release their trigerminal potential inherent in the nuclei, a chain of events is set into motion which results in the development of embryonic tissue. According to Melicow the final outcome of the neoplasia would then be classified as embryoma, choriocarcinoma, embryonal carcinoma, teratocarcinoma and adult teratoma. Overlapping of the cellular types may occur and there is considerable variation in their histological structure.

From a clinical standpoint several factors should be emphasized. Despite the rarity of testicular lesions, a careful examination of the scrotal contents in infants and children should be a routine part of the physical examination. Involvement of the testes by neoplasm results in diffuse enlargement of the organ without nodularity or irregularity in its general outline. Unless the tumor is of such size as to be evident by observation alone, its presence often goes undetected. Even the child's mother more often than not is unaware that the organ has become enlarged until her attention is attracted to it by other factors. The history of a bruise to the scrotum a few days prior to the examination, resulting in painless enlargement of the testicle, is the common denominator of many case histories studied. This was true for both youngsters who came under our observation. An associated hydrocele in 20 to 25 per cent of testicular tumors [*3*] may also tend to mask their presence and delay the institution of immediate and specific therapy. Although there is no agreement as to the relationship between cryptorchidism and tumor in children, the statistics reported by Warres [*26*] indicate that

in the adult the incidence of malignancy may be twenty to forty times as great in the undescended testis as in the normal testis.

Urinary gonadotropin similar to that developed during pregnancy may be liberated by some testicular tumors [*17*]. The cytotrophoblast cells which are found in the malignant teratoid growths are probably responsible for its production. The presence of both chorionic and pituitary gonadotropin has been identified; and although its physiological significance is still not clearly understood, the gynecomastia which has been reported as accompanying testicular lesions is probably the reflection of this hormonal activity [*14*].

Differential diagnosis of testicular enlargements must include hematoma, hydrocele, spermatocele, benign lesions (also rare) and the granulomatous diseases, as well as secondary growths [*14*]; however, in consideration of the unpredictable and potentially virulent characteristics of the teratoid group of tumors, it is wise to consider all testicular enlargements in children as being malignant until proved otherwise by microscopic confirmation. Whether or not biopsy is warranted prior to complete orchiectomy is perhaps a matter of individual surgical thinking. It is our opinion, however, that when a solid tumor of the testicle is encountered in an infant or child, it is best handled by complete removal of the affected organ with high ligation of the spermatic cord. The administration of postoperative roentgen therapy is not without risk, and careful consideration should be given before it is utilized. Sterilization of the opposite testis and destruction of epiphyseal growth centers may inadvertently result from this treatment. Rusche is skeptical that roentgen therapy is actually of much value in this type of growth. There is no convincing evidence in the literature to substantiate the belief that its use is justifiable. Although it is generally accepted that some testicular tumors are radiosensitive, the exact intensity of their invasive properties is probably dependent on an inherent nuclear potential, a property which cannot be predicted by a study of their microscopic configuration. Regardless of our desire for didactic reasoning, the degree of malignancy or benignity of individual teratoid tumors is not reflected in the mere formality of classifying them according to histological types. Approximately 35 per cent of tumors diagnosed as being malignant result in death to the host following surgery, regardless of whether or not radiation was administered as supplementary therapy. It seems practical to us to reserve radiation only for those lesions which have broken through the confines of the tunica albuginea and extended beyond the testicle itself, or for those of a highly malignant cellular pattern. In the case of embryonal carcinoma reported herein radiotherapy was not employed and the patient is alive and well without evidence of recurrence three years following simple orchiectomy.

CONCLUSIONS

Testicular tumors in infancy and childhood are rare lesions. They originate from the totipotent sex cells which are capable of producing tissue representing any or all derivatives of the three primary germ layers. Two case reports are presented, one representing a so-called benign growth, the adult teratoma, and the other a malignant neoplasm, the embryonal carcinoma. A brief discussion of the interesting features of this group of tumors is given.

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Clinical Arteriosclerosis Obliterans

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ARTERIOSCLEROSIS obliterans is a degenerative, obstructive arterial disease process which occurs most commonly in men from the fourth decade on, occasionally complicated by hypertension, diabetes mellitus or both. There are many signs and symptoms of the disease, which may be present singly or in combination; these include intermittent claudication, coldness, numbness, rest pain, burning paresthesia, ischemic neuritis, pallor on elevation, rubor on dependency, excessive sweating, trophic skin changes, ulcer and diminished or absent dorsalis pedis, posterior tibial, popliteal, femoral and even abdominal aortic pulsations.

Medical treatment consists of education as to care of the feet, with utilization of measures designed to increase nutrition to the part by vasodilatation. Patients must be admonished that because of diminution in the blood supply to the feet, continued special care is necessary to prevent serious difficulties. The feet must be washed each night with mild soap and warm water. The spaces between the toes are to be handled gently but thoroughly. After drying the feet carefully, vaseline or lanolin ointment is gently massaged into the skin. The feet must be kept warm at all times using clean woolen socks changed daily during the winter and white cotton socks in warm weather. Long, heavy underwear should be worn. The feet must be protected from injury at all times, this being facilitated by wearing properly fitting shoes. Loose-fitting bed socks should be worn at night. Since the circulation is already compromised, no unnecessary demands should be made upon it by injudicious use of hot water bottles or electric heating pads. Toenails should be cut straight across, in a good light and after the nails have been softened by soaking the feet in warm water for twenty minutes. No self-surgery on corns or calluses is permitted. The diet should include 3 to 4 quarts of water daily, liberal quantities of fresh vegetables and strict adherence to diet if the patient is diabetic. Tobacco is interdicted, circular garters are not to be worn, and if anything unusual develops such as a blister, infection or worsening of symptoms, a physician is to be consulted immediately. In addition to these common sense measures an endeavor should be made to secure vasodilatation, either indirectly or by therapeutic amounts of whiskey, glycine powder, arlidin, priscoline® or dibenzyline.® It has been recorded that when a sympatholytic drug is given by mouth or parenterally, an adverse effect may be produced. Blood flow follows the path of least resistance, so that when general vasodilatation is produced more blood will flow into the healthy than into the diseased arteries, thereby further reducing an already impaired blood supply [*1*]. Learmonth [*2*] has stated that there is not as yet a suitable sympatholytic drug and decries the intra-arterial injection of these drugs.

The natural history of arteriosclerosis obliterans does not follow a standard pattern. In some patients the disease once having manifested itself continues on its inexorable course producing incapacity, loss of limb and even life. In others there is a spontaneous improvement which may take place under excellent conservative medical management and in some patients who have not availed themselves of

specific medical counsel. Just how much benefit should be attributed to medical therapy is an insoluble problem. In discussing gradual improvement over a long period of time in a patient taking a vasodilating drug, Cranley [3] states that evaluation is difficult since there is at present no known investigative method which will delineate improvement as spontaneous or directly attributable to the medication used.

There are many factors which enter into the assessment of a patient with arteriosclerosis obliterans, such as age, sex, race, diabetes mellitus, hypertension, tobacco, trauma, malnutrition and congestive heart failure. The one which most affects the prognosis is in all probability diabetes mellitus. For one thing, arteriosclerosis obliterans occurs most frequently in diabetic persons; therefore it may be stated that there are many arteriosclerotic patients who do not have diabetes, but most patients with diabetes have arteriosclerosis. The earlier onset of arteriosclerosis obliterans in persons with diabetes makes the clinical picture vastly different, albeit the pathologic lesions do not contrast markedly with those seen in patients without diabetes. The arterial disease is often of a more fulminant type, an infectious component frequently presents, gangrene is a very serious problem with a systemic response being elicited, and healing is very difficult to achieve. Occasionally the one redeeming feature of being a diabetic person with arteriosclerosis obliterans is that when the process occurs in a young individual and amputation is necessary, it can be done at a lower level with reasonable assurance that the stump will heal and higher reamputation will not have to be performed later. Of course the factors operating originally which necessitated the primary amputation may intervene again and require a secondary amputation.

The pathologic process differs from individual to individual with varying degrees of thinning and degeneration of the tunica media, different gradations of atheroma and calcium deposition, producing hemorrhage and thrombosis of variable dimensions. Much is known of cholesterol and lipoid metabolism, but we have not been able to translate our studies to date into a therapeutic approach with predictable results.

The signs and symptoms of arteriosclerosis obliterans are directly related to ischemia, i.e., inadequate arterial circulation. The process may be mild, moderate or severe. In some patients the disease is sharply delimited with few if any clinical manifestations; in others it is so widespread as to constitute a threat to limb, life or both. Arteriosclerosis obliterans is a very interesting disease process to study, not only because the problems it presents tax the ingenuity of the clinician but also because the unpredictable exacerbations and remissions, spontaneous or induced, require constant attention so that a false sense of security is not created.

Arteriosclerosis obliterans is not an acute pathologic process, but rather a slowly developing disease which may never produce signs or symptoms severe enough to direct the patient to his physician. A routine physical examination may disclose absent or impaired pulses, loss of hair on the dorsal aspect of the toes, thickened bizarre toenails, thin atrophic skin, or cold, blue, wet feet. With any or all of these signs, a patient may deny any symptoms referable to his circulatory system. Conversely, examination may reveal apparently normal findings as to pulses present, appearance of the skin and nails, with no evidence of atrophy or abnormal vasomotor or sudomotor activity, yet the patient's complaints lead to the inescapable conclusion that here in its incipiency is an organic arterial disease process. The fine line that separates the viable, adequately nourished limb from that in which there is impending death of tissue due to ischemia can be erased by even minor trauma. This trauma can be initiated by a hot water bottle, electric heating paid, ice bag, cutting the skin while trimming a toenail, the application of an escharotic to lift out a corn, removal of an ingrown toenail and a host of other procedures which in themselves are innocuous but which if performed on an ischemic extremity can be lethal to it.

A patient with arteriosclerosis obliterans can become a medical emergency by the lodgement of an embolus producing acute and severe ischemia distal to the occlusion. Thrombotic occlusion is more gradual in nature, there usually being ample opportunity for collateral circulation to dilate and hypertrophy and to assume the function of supplying nourishment before the obstruction becomes complete. In the former circumstance embolectomy where size of the vessel permits is the treatment of

choice; in the latter, wider latitudes are enjoyed and employed. There should be no controversy as to medical versus surgical therapy. Any medical man with a surgical conscience, or vice versa, knows that one complements the other, so that a surgical-medical team is necessary to prepare the patient for surgery, perform the operative procedure and then regulate the postoperative treatment.

The patient with intermittent claudication, cold feet which may be described as being "icy," numbness on sitting or lying down, or mild rest pain can be treated by conservative medical measures designed to produce vasodilatation. When the ischemia produces nutritional failure, which may be characterized by burning paresthesias, intractable rest pain, ischemic neuritis, pallor on elevation, rubor on dependency with excessive sweating all superimposed on the symptoms previously mentioned, more definitive measures are indicated. To assist in the establishment of a program of treatment tailored to the individual needs of the patient in question, special investigative studies must be instituted.

First and foremost, the patient must receive a good physical examination. Electrocardiograms are done on all patients. In determining the presence or absence of pulses it is prudent to recall that the dorsalis pedis pulse is absent in 12 per cent of normal subjects. Collateral pulses should be sought, particularly the anastomotica magna artery on the anterior aspect of the internal condyle of the femur, which is a branch of the superficial femoral artery; and when the dorsalis pedis pulse is absent, its function is usually performed by the peroneal artery, a branch of the posterior tibial. Studies of skin temperature are of value when taken under basal conditions and repeated to rule out errors. Skin-toe temperatures may vary from 24° to 32°C., depending on conditions existing at the time of the study. Of significance is a 1 to 2 degree difference in digits of the same or opposite foot. The reflex vasodilatation test can be utilized advantageously to indicate the immediate effect of lumbar sympathectomy as well as to point out the long-term outlook. As to oscillometry, no information can be gained by utilization of this device that cannot be duplicated by a well trained, sensitive examining finger. Plethysmography can be employed to measure blood flow to a part, but the results obtained are of more significance from a statistical than a clinical standpoint. A method of investigation which has assumed increasing importance not only in facilitating diagnosis but also in permitting more definite plans for treatment is the injection of radiopaque dye intra-arterially. The information thus gained can be obtained by no other method. Collateral circulation is outlined, the site of the obstructive process is localized, and the proximal and distal portions of the vessel can be visualized and evaluated as to surgical intervention.

The treatment will vary from patient to patient, depending on the site of the lesion, how extensive it is, the status of the collateral circulation as well as that of the vessel proximal and distal to the obliterated segment, and the general over-all condition of the patient. Formerly, many patients were refused lumbar sympathectomy solely on the basis of age; different age levels were imposed by different clinics, but the dividing line was usually age sixty. The literature of the 1940's was filled with contraindications to lumbar sympathectomy, and frequently mentioned was the age factor. Today the age limit has been advanced, so that in certain selected cases patients in their seventies and even eighties are considered as candidates for the operation. Spontaneous sympathectomy has been reported by Goetz [4], who postulates this phenomenon on the basis of an inflammatory reaction or ischemia of the nerves, thereby depriving the blood vessels of sympathetic innervation. Since spontaneous denervation cannot be anticipated, it goes without saying that surgery must be performed when indicated. If our objective is to achieve vasodilatation localized to an extremity, it is well to remember Learmonth's [2] admonition that this can be most effectively produced only by sympathectomy. Thromboendarterectomy is of limited appeal. It can be used alone, but therapeutic effectiveness is greatest when it is combined with sympathectomy or when used to prepare either the proximal or distal host vessels, or both, for vessel grafting. After much trial and error and many false starts blood vessel grafting has finally come of age. Arterial continuity can be restored with autogenous venous grafts, homologous arterial grafts or synthetic fabric grafts fashioned from nylon, orlon, vinyon-N or dacron.

To explore completely all therapeutic ap-

proaches to arteriosclerosis obliterans is beyond the scope of this paper. To keep the discussion within bounds it will be restricted to lumbar sympathectomy. This operation is indicated in the following circumstances: in the presence of high vasomotor tone, when mild rest pain is relieved by medical vasodilating procedures, when distal pulses disappear with exercise sufficient to cause claudication, when a single toe must be amputated and where the aortogram or laparotomy indicates that vessel grafting is not feasible. Trophic skin changes indicating failing peripheral nutrition can be benefited by sympathetic denervation.

A series of twenty-five conventional lumbar sympathectomies in which the second and third lumbar ganglia were removed was reported in 1952 [5]. Seventeen patients had good results and eight patients had bad results, including two with ulcers that failed to heal, and six who had amputations of the lower third of the thigh. Since 1953 the operation has been modified so that the twelfth thoracic ganglion and the first, second and third lumbar ganglia [6] are extirpated through an incision which in some instances employs partial resection of the twelfth rib. If the ganglia cannot be identified, then following Slessor's [7] recommendation 10 cm. of chain are removed. Of the last twenty-five patients to undergo this modified procedure, twenty had good results and five had bad results; all ulcers healed and there was but one amputation, involving the lower third of the thigh. Interestingly, twenty-one patients had absent distal pulses preoperatively, and following surgery there was a return of pulses in nine. To evaluate patients after sympathectomy is a rather difficult task. Too much emphasis must be placed on subjective rather than on objective findings. In this study claudication, coldness, numbness and rest pain were used as criteria, and the return of pulses, healing of ulcers and necessity of amputation were used as complementary additives. No patient's condition was made worse by operation. Learmonth [2] and Slessor [7] have stated that when the viability of a limb is in doubt, it is to the patient's advantage to delay operation until such time as nutritional improvement occurs. In the event that the operation is performed too soon, edema may occur in the doubtful tissue which may precipitate gangrene or extend that which is already present, and the fate of the extremity will be sealed.

Lumbar sympathectomy, properly executed in well selected patients, produces local vasodilatation which should maintain the cutaneous circulation and obviate gangrene. Spontaneous improvement in patients with arteriosclerosis obliterans makes evaluation of various therapeutic approaches difficult. The longer a patient suffers from diabetes the more prone he is to have arteriosclerosis obliterans, and the combination of the two invariably leads to vascular complications. This study would seem to indicate that the extent of sympathetic denervation is related directly to the end result achieved.

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Subdiaphragmatic Abscess

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AN inflammatory process or accumulation of purulent material in the subdiaphragmatic spaces represents one of the important serious complications of abdominal disease. Fortunately the condition is relatively uncommon. There are several factors which increase the danger of infection in this region. They are: (1) the unique location of the subdiaphragmatic region which serves to complicate the surgical approach; (2) the technical problem of establishing and maintaining drainage of this area; (3) the difficulty in diagnosis; (4) the infrequency of the complication which decreases the chance of early recognition; (5) the diaphragmatic motion and subdiaphragmatic pressure changes which influence the progress of healing of an infection in this area; and (6) the close proximity of the liver to the pleural cavity which makes this location a hazardous one when infection occurs.

The clinical material which forms the basis of this study comprises forty-one cases from the Albert Einstein Medical Center, Northern Division. Of this total, ten cases were found between the years 1929 to 1935. These were all cases in the pre-antibiotic era. The remaining thirty-one cases, treated between 1935 and 1955, comprise those which, when recognized, benefited by the use of sulfa drugs or antibiotics, or both.

PATHOGENESIS

The subphrenic space may be involved by the following: (1) Invasion from the immediate vicinity by direct spread of infection as from perforated peptic ulcers and ruptured gallbladder, or (2) distant extension. Distant intraperitoneal foci of infection can infect the subphrenic region by direct intraperitoneal drainage of infected material by way of the gutter between the ascending colon and the lateral parietal peritoneum to the region of the right kidney and then to the subdiaphragmatic area. (3) Rupture of an abscess into the subphrenic space. (4) Extension from the thorax. This is not a common source of subphrenic infection, although it certainly does occur. (5) The blood stream. In these cases the subphrenic infection is a metastatic infection resulting from some distant infective focus. (6) Direct implantation. By this method, organisms are implanted directly in the subphrenic region, such as through a puncture wound or by an aspirating needle. (7) The lymphatics. The inferior and superior surfaces of the liver are richly supplied with lymphatics. Lymphatic channels have also been observed to pass from the liver to the diaphragm.

DIAGNOSIS

Subdiaphragmatic abscess remains a serious complication in abdominal surgery because of the difficulty in diagnosis. The disease is recognized too late. Gatewood [4] believed that subphrenic abscess should be considered in any patient not doing well after an abdominal operation, even though surgery was performed months previously. "Signs of pus somewhere, signs of pus nowhere else, signs of pus there" was Barnard's [1] aphorism.

The disease can be recognized more easily if the condition is kept in mind. Correct diagnosis is based on the following observations:

History of Operation. If the patient has an unsatisfactory period of convalescence with persistence of unexplained fever, subphrenic abscess should be suspected.

Clinical Findings. The patient may show toxemia, secondary anemia, leukocytosis, and elevated temperature, pulse and respiration. A significant sign in early diagnosis of subdia-

phragmatic abscess is tenderness over the subdiaphragmatic space. Involvement of the anterior space on either side usually permits an early diagnosis, since these regions are more directly accessible to palpation.

Early tenderness may also be found in the region of the eleventh and twelfth rib on the involved side, and such tenderness may be minimal and sharply localized. Pain above the clavicle is known as Kehr's sign and is due to irritation of the diaphragm. Basilar atelectasis on the side of the abscess soon appears, but is often minimal. In subdiaphragmatic abscess there is often concomitant basal pleurisy, pleuropneumonia or a pleural effusion. Physical examination may show elevation of the dome of the diaphragm and diminished diaphragmatic motion.

Roentgenographic Aid. The x-ray examination is most valuable in the diagnosis and confirmation of the accuracy of the physical findings.

In studying a patient suspected of having a subphrenic abscess, fluoroscopic and radiologic examination of the chest and abdomen should be performed, with the patient in both the recumbent and the erect positions. Posteroanterior and lateral films of the thorax should be made, including high contrast studies with the Bucky diaphragm. Films of the abdomen should include the diaphragmatic area with the patient erect. Particularly when the left diaphragmatic area is suspect, barium sulfate should be administered orally to demonstrate displacement of the stomach. Occasionally kymography and diagnostic pneumoperitoneum may be indicated. One of the early evidences of subdiaphragmatic abscess is restricted mobility of the involved hemidiaphragm. This can best be demonstrated fluoroscopically. Elevation and fixation of the diaphragm occur later, more prominently and more readily evident on the right side. Particular attention should be directed to the posterior aspect of the right hemidiaphragm, which normally slopes acutely from its convexity. With abscess in the postsubhepatic space, this slope is reduced and may be completely eliminated.

As a result of lymphatic extension of the infection, a basilar pleural effusion occurs, obscuring the costophrenic sulcus. This probably accompanies all suprahepatic abscesses. In 2 per cent of cases [3] the abscess was visualized as an air-fluid accumulation in the subdiaphragmatic space.

Artificial pneumoperitoneum for the diagnosis of subdiaphragmatic abscess is sometimes helpful. This can be done by injection of 750 to 1,000 cc. of air followed by x-rays taken with the patient in the upright position. If the diaphragmatic area is free, the air can be seen separating the liver on the right and the stomach and the spleen on the left from the diaphragm above. If an abscess has formed between the diaphragm and liver, however, air collects below the liver, and no clear spaces can be demonstrated between the liver and diaphragm, due to the inflammatory process and adhesion between liver and diaphragm. This also applies to the left side, where, if an abscess forms, no air collects between the stomach below and the diaphragm above.

Aspiration. Diagnostic needle aspiration may spread infection to the pleura or peritoneum. It may also damage intra-abdominal viscera. It may be done immediately before operation, and the needle left in place until the pus has been drained. Aspiration may also be considered in a very toxic patient in whom operation could be fatal.

TREATMENT

Early and efficient treatment when the disease is suspected is of great value in management. Any predisposing cause must be treated thoroughly in order to obtain the best result and prevent relapse. Serious complications of subdiaphragmatic abscess may be prevented by: (1) careful walling off of the primary infection during the operation; (2) complete aspiration with suction of all fluid or pus found in the peritoneal space and over the dome of the liver; (3) adequate drainage of the peritoneal cavity; (4) adequate chemotherapy postoperatively; and (5) the use of Fowler's position if indicated.

Chemo- and Antibiotic Therapy. Since the majority of subphrenic infections do not go on to suppuration, these infections may be treated by conservative measures, especially making use of modern chemotherapy. The common causative organisms are Bacillus coli, streptococci and staphylococci. Penicillin and streptomycin should be effective, but if used with no response, chloromycetin,® aureomycin® or other modern broad-spectrum antibiotics must also be used. If there is no improvement and the

patient shows signs of deterioration and increase in white blood cell count, despite antibiotics, a suppurative process must be suspected. Surgical intervention and drainage is then necessary. However, under intensive chemotherapy and antibiotics, there may be an apparent improvement, evidenced by a lowered temperature and white blood cell count. This may completely overshadow an almost imperceptible but steady decline in the general health of the patient. If this continues for many weeks, masking the true course of infection, suddenly the abscess may rupture through the diaphragm into the thorax, establishing widespread pleural contamination and intrapulmonary infection. Since modern chemotherapy may mask the usual symptoms of an abscess, careful observation is mandatory, even though the patient is apparently responding well to chemotherapy and antibiotics as evidenced by the usual clinical signs. If any sign of suppuration occurs, surgery is necessary.

Surgical Treatment. The surgical approach to an abscess depends upon the location of the infection. There are three approaches: (1) transthoracic (transpleural), (2) transperitoneal and (3) extraserous.

Ochsner and DeBakey [7] and Faxon [2] have said there is no longer any justifiable reason for using an approach other than the extraserous because although contamination can occur (with 62 per cent mortality), the mortality is only 24 per cent if neither cavity is contaminated. Ochsner and DeBakey had a mortality rate of about 45 per cent with the transerous approach and about 10 per cent with the extraserous.

Method of Approaching the Abscess Due to Location. Posterior space: There are two ways of approaching this space:

1. *Transpleural:* Posterior resection of the eleventh rib may be performed. The lower costophrenic reflection of the pleura and of the diaphragm are then crossed. This transpleural approach to the subdiaphragmatic space is satisfactory and direct, but considerable care must be taken to prevent contamination and pneumothorax. If the pleural space has not already been obliterated by the inflammatory reaction, it must be done in one of two ways: (1) place a firm gauze pack against the exposed parietal pleura and leave it in place for forty-eight hours, or (2) suture together with very fine interrupted sutures, placed around the entire periphery, the exposed pleura, and the pleura and the diaphragm, thus forming a sinus directly into the abscess.

Packing the pleura has the disadvantage of making a two-stage procedure of the operation with a delay of several days before the fluid drainage can be accomplished.

2. *Extraserous:* Resection of the twelfth rib or the extraserous approach is advocated by Ochsner and DeBakey. This technic consists of resection of the entire twelfth rib and division of the underlying fibers of the diaphragm and fascia in order to permit access to the retroperitoneal space. From this point, the abscess can be reached and entered directly by blunt dissection along the peritoneal surface. In dividing the fascia, care should be taken to make the incision horizontally at the level of the first lumbar spinous process rather than obliquely along the bed of the twelfth rib, as failure to observe this precaution may result in a disastrous contamination of the pleural cavity. Melinkoff [6] demonstrated in a cadaver that the pleura on the right side extends to below the twelfth rib in 62 per cent of all cases but is never found as low as the level of the first lumbar spinous process.

The alternative approach by resection of the twelfth rib and operating entirely extrapleurally overcomes the difficulties of the transpleural method, but has the disadvantage that from this lower level a long distance is required to reach and maintain drainage.

Anterior space, extraserous approach: Infections in the anterior space can be drained satisfactorily by a subcostal incision, which is relatively simple. Incision is made 1 inch below the costal margin, extending from the mid-rectus laterally and downward about 3 inches. This incision is deepened through all layers to the transversalis fascia. The blunt dissection is then carried upward under the surface of the ribs in order to keep within the walled-off area and to avoid entering the peritoneal cavity. The peritoneum is pushed away from the diaphragm until the abscess is reached.

Aspiration. Ordinarily treatment by aspiration is not considered, but Krough [5] reported that he had used it with satisfactory results in the treatment of amebic subphrenic abscess at Guy's Hospital as a routine procedure.

In a very poor risk patient, in whom an

unsuccessful operation would weigh the scale heavily, aspiration might be indicated.

General Management. In addition to antibiotics and surgical treatment, it is important to maintain protein and electrolyte balance. Blood transfusions are used as required. A nourishing diet of high protein value, breathing exercises and careful nursing all help to hasten recovery.

TABLE I
SOURCES OF SUBDIAPHRAGMATIC ABSCESS

Source	No. of Cases	Approximate Percentage
Gallbladder	11	26.4
Stomach-duodenum	8	19.2
Colon	7	17.0
Appendix	4	11.0
Pancreas	2	4.8
Uterine tube	2	4.8
Chest	2	4.8
Small intestines	2	4.8
Spleen (septic emboli)	1	2.4
Blood-borne (gangrene of foot)	1	2.4
Kidney	1	2.4
Total	41	100

TABLE II
EXAMINATION OF ORGANISMS

Organism	No. of Cases	Approximate Percentage
Bacillus coli	7	41
B. coli and streptococcus	3	17
B. coli and proteus	2	12
Streptococcus	1	6
Streptococcus and staphylococcus	1	6
Sterile	2	12
Other	1	6
Total	17	100

CLINICAL DATA

Between the years 1929 and 1955 there were forty-one reported cases of subdiaphragmatic abscess at the Albert Einstein Medical Center, Northern Division. (Table I.) Of these, ten patients were treated between 1929 and 1935 before sulfonamides and antibiotics came into general use. Five cases were diagnosed before death, and five were unrecognized until autopsy examination was performed. The mortality in the preantibiotic group was 100 per cent in the unrecognized cases. (Table II.) Of the five patients operated upon, one survived and four died. Between 1935 and 1955 a total of thirty-one cases was reported. Of these, eleven were unrecognized and twenty were diagnosed. In all of the unrecognized cases the diagnosis was established by autopsy. Of the patients diagnosed as having subdiaphragmatic abscess, sixteen were operated upon. Twelve patients survived and four died. Four patients were treated with antibiotics alone; one of these survived and three died.

TABLE III
CLINICAL FINDINGS

Findings	No. of Cases	Per cent
White blood cell count above 12,000	36	76
Polymorphonuclear cells over 75 per cent	38	80
Local pain and tenderness	39	82
Fluid in chest	20	42
Hiccough	2	4
Pneumonitis	15	32
Displacement of heart	4	8
Elevation and limited motion of diaphragm	14	29
Septic temperature above 101°F	41	100

TABLE IV
X-RAY FINDINGS

X-ray Findings	No. of Cases	Per cent
Diaphragm:		
Elevated or fixed	14	28
Not visualized	4	8
Obliteration of costovertebral angle	3	6
Basal pneumonitis	16	42
Fluid in chest	20	32
Displacement of heart	4	8
Air and fluid level under diaphragm	9	36

For the most part these patients presented a toxic appearance (Table III), and those who had had previous operations did not do well in the postoperative period. High fever, leukocytosis, prostration and malaise developed,

and reflex ileus occasionally occurred. Some of the patients had pain in the upper abdomen or in the region of the eleventh and twelfth ribs. Hiccough was observed in three cases. Referred pain to the shoulder and back were also found. X-ray examination frequently showed basal pneumonitis or an elevated dome of the diaphragm with obliteration of the costophrenic angle. (Table IV.) Associated pleural effusion was commonly found with the disease.

TABLE V
COMPLICATIONS

Complications	No. of Cases	Approximate Percentage
Basal pneumonitis	15	36
Atelectasis	1	2.4
Pleural effusion	20	32
Empyema	4	10
Septicemia	1	2.4
Pericardial effusion	1	2.4
Perforation of diaphragm	1	2.4

In this series the youngest patient was seven years old. The average age was forty-eight years, and it was found that the highest incidence of subdiaphragmatic abscess occurred between the fifth and seventh decades. There were twenty-two males and nineteen females.

The location of subdiaphragmatic abscess was found to be as follows:

Right side, 82%	
Right posterosuperior,	26%
Right anterosuperior,	10%
Right inferior,	20%
Right posterosuperior and right inferior,	18%
Right anterosuperior and right inferior,	8%
Left	6%
Combination of left and right	12%

The diagnosis of subdiaphragmatic abscess in our series of forty-one cases was frequently missed. Sixteen cases (39 per cent) were unrecognized until time of death, and twenty-five cases (61 per cent) were diagnosed. Twenty-one patients (51 per cent) were operated upon, in one of whom no pus was obtained. Thirteen patients (62 per cent) survived after operation, and eight died (38 per cent). Of the four patients who did not undergo operation, one (25 per cent) survived with the use of antibiotics and chemotherapy, and three (75 per cent) died. (Table V.)

Of our twenty-one operated cases, the surgical approach was transperitoneal in eighteen, extraserous in four, and transpleural in two. In four of these cases the abscess was found at the time of operation for the primary lesion.

CASE REPORTS

In this series, several types of therapy were compared. The most successful method was the combination of antibiotic therapy and surgical drainage. The following case is reported as a typical example showing the development of an abscess and its successful treatment by antibiotics and surgery.

A sixty-two year old man was admitted to the Albert Einstein Medical Center, Northern Division on November 1, 1954, with a diagnosis of chronic calculous cholecystitis. Cholecystectomy, appendectomy and removal of a retroperitoneal lipoma were performed on November 3rd. The patient was given 2 cc. of dicrysticin® (2 cc. contains 400,000 units of penicillin and ½ gm. of streptomycin) every twelve hours postoperatively. The immediate postoperative period was uneventful except for a low grade temperature of 100°F.

On November 7th occasional hiccough developed. There was a little fullness and tenderness at the right upper quadrant of the abdomen and some bile drainage from the wound.

On November 8th hiccough stopped, but the patient became febrile. The temperature was 101°F. at 8:00 P.M. and rose to 102°F. at midnight. The leukocyte count was 22,300 cells per cu. mm. of which 89 per cent were polymorphonuclear cells. X-ray examination of the chest showed moderate elevation of the right leaf of the diaphragm and the probable presence of an abnormal subdiaphragmatic collection. Achromycin, 250 mg. every six hours, was given by mouth in addition to dicrysticin.

On November 9th his temperature remained at 102°F. The patient appeared toxic. Leukocyte count was 20,800 with 91 per cent polymorphonuclear cells. The diagnosis of subdiaphragmatic abscess was made. Drainage was instituted that afternoon. The extraserous approach after resection of the twelfth rib was used. The subhepatic and subdiaphragmatic regions were explored by finger dissection. Some adhesions were broken and some serosanguinous fluid was evacuated. Drains

were placed in the subdiaphragmatic and subhepatic spaces. Culture of the fluid showed B. coli. After drainage, the patient was given 2 cc. of dicrysticin, and 500 mg. of achromycin were administered intravenously.

On November 10th his temperature varied between 103° and 104°F., the pulse rate was 120 per minute, and respirations were 26 per minute. The leukocyte count was 28,400 per cu. mm. with 91 per cent polymorphonuclear cells, which showed toxic granulation. There was a fair amount of drainage from the subdiaphragmatic region. The patient had occasional attacks of hiccough.

On November 12th the patient showed improvement. His temperature fell to normal. Hiccough stopped, and the intravenous administration of achromycin was discontinued. Oral achromycin was substituted thereafter. Convalescence was uneventful, and the patient was discharged on November 25th.

The following case demonstrates the successful treatment of a subdiaphragmatic abscess by antibiotics alone.

A forty-two year old man was admitted to the Albert Einstein Medical Center, Northern Division, on August 17, 1952, with a diagnosis of chronic calculous cholecystitis. Cholecystectomy and choledochostomy were performed on August 18th. Twelve hours after operation re-exploration was performed because of internal hemorrhage. During the postoperative period the patient received 1 cc. of combiotic® (a penicillin and dihydrostreptomycin preparation) and 600,000 units of crysticillin® (a procaine penicillin G preparation) every twelve hours. His temperature was normal by the fifth postoperative day (August 24th).

On August 25th the antibiotic therapy was stopped. That afternoon diffuse abdominal cramps and diarrhea developed; his temperature was 102.40°F. Antibiotics were given again and the temperature became normal. Diarrhea subsided by August 26th.

On August 27th the patient complained of pain in the right upper quadrant of the abdomen and right shoulder made worse by deep breathing. His temperature rose to 102°F., the pulse to 120 per minute, and the respiratory rate to 32 per minute. There was marked tenderness and rigidity in the right upper quadrant of the abdomen. The leukocyte count was 58,250 per cu. mm., of which ninety-seven per cent were polymorphonuclear cells; many showed toxic granulation. X-ray examination showed air under the right diaphragm. The original antibiotic therapy was stopped, and an intravenous infusion containing oxytetracyclin (1 gm. every twelve hours) was started.

On August 29th the temperature dropped to 100.6°F., and the pulse rate to 100 per minute. There was less tenderness and pain in the right upper quadrant of the abdomen. X-ray at this time demonstrated fluid in the right costophrenic sulcus. The liver shadow appeared to be increased in size, and again there was air under the diaphragm. Definite diagnosis of subdiaphragmatic abscess was made. The patient was continued on intravenous oxytetracyclin (500 mg. every twelve hours) until September 4th. Oral administration was then substituted in a dosage of 500 mg. every six hours.

On September 6th the temperature returned to normal and the leukocyte count fell to 17,000 cells per cu. mm. The patient was discharged on September 9th.

CONCLUSIONS

Subdiaphragmatic abscess is not a common condition, and probably with the increasing use of chemotherapy and antibiotics it will become even rarer. Subdiaphragmatic abscesses are secondary to infections in many parts of the body, but the great majority follow intra-abdominal disease or operation. The control and prevention of peritonitis could therefore reduce the incidence of this complication. Subdiaphragmatic abscess is a serious complication when it occurs. It prolongs the period of hospitalization anywhere from two weeks to three months, and is often fatal. The seriousness of this disease is increased by difficulties in diagnosis. Often the condition is not recognized early enough to permit effective therapy. However, if it is kept in mind, the diagnosis can be made. All patients with an unsatisfactory convalescent period after surgery on the abdomen should be suspected of having a subdiaphragmatic abscess. The use of antibiotics and chemotherapeutic substances can obscure the true status and progress of the abscess, and allow more serious complications to develop. The patient should, therefore, be observed carefully even if antibiotics are used.

Surgical drainage is indicated when a fluid collection occurs. Operation should not be delayed, as this increases the mortality rate. The extraserous approach to the subdiaphragmatic abscess is recommended. A combination of antibiotics and surgical drainage is often the most satisfactory method of handling these cases.

Complications of subphrenic abscess play a great role in the morbidity and mortality of this disease. The great majority of complications are intrathoracic. Excluding from con-

sideration the primary process, the prognosis for the patient with a subdiaphragmatic abscess is influenced by several factors. Delay in diagnosis, treatment and the presence of complications have a profound bearing. The earlier diagnosis is made and treatment instituted, the less chance there is for a complication to develop and the better the prognosis. The axiom, "Sign of pus somewhere, sign of pus nowhere else, sign of pus under the diaphragm," should be kept in mind when we are dealing with patients who have undergone abdominal surgery.

SUMMARY

This study presents a review of the history, pathogenesis, diagnosis, treatment and complications of subdiaphragmatic abscess.

An investigation of forty-one cases which occurred during the last twenty-five years at the Albert Einstein Medical Center, Northern Division is included.

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Renoduodenal Fistula

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FISTULAS between the kidney and duodenum have been reported several times. Most are secondary to surgery; Schneider [1] estimates that seven of every 1,000 right nephrectomies will be followed with this complication. Spontaneous renoduodenal fistula is rare and is nearly always secondary to renal disease [2]. Because of the rarity of this type of fistula and the difficulty in diagnosis and management, a case of renoduodenocutaneous fistula is worth reporting. This fistula followed the drainage of a perinephric abscess. It persisted for over three years and was successfully managed by right nephrectomy and closure of the duodenal fistula.

CASE REPORT

R. H. (No. 51-2522) was admitted to the St. Francis Hospital with a three-year history of severe, constant pain in the right flank and lumbar spine, with drainage from a small sinus in the right flank for two and a half years. Six months after the onset of pain, studies at another hospital showed a perinephric abscess, for which incision and drainage was carried out. The wound healed and the patient was discharged after two weeks; however, two months later the incision spontaneously opened and again drained purulent material. Lumbar back pain persisted over the next two years, associated with a weight loss of 70 pounds. The wound drained intermittently on several occasions. Drainage was never copious and on each occasion was decreased by antibiotic therapy.

In May, 1950, a definite communication between the sinus in the right flank and duodenum was demonstrated (Fig. 1), but no attempt at closure was made. At a second hospital, in October, 1950, and again in April, 1951, attempts were made to close this fistula through anterior abdominal approaches but these were abandoned because of vascular adhesions; a gastroenterostomy was performed. However, back pain and two small draining sinuses persisted until the patient was admitted to the St. Francis Hospital on July 19, 1951.

Physical examination showed a chronically ill, markedly underweight thirty-nine year old white man with two right anterior abdominal scars and a scar in the right flank, in the midportion of which was a draining sinus exuding a small amount of serosanguineous material. There was a slightly tender mass measuring approximately 15 by 20 cm. in size in the right upper quadrant of the abdomen. The prostate was normal and the remainder of the examination was entirely negative except for loss of normal lumbosacral curvature of the spine.

Laboratory studies showed a hemoglobin of 11 gm. per cent, white blood cell count 10,700 per cu. mm. with a normal differential. Serology and urinalysis were negative. The total protein was 5.9 gm. per cent, with albumin 3.8 gm. per cent. The blood urea nitrogen was 10.6 mg. per cent, cephalin flocculation 3 plus, alkaline phosphatase 37.4 Bodansky units, and acid phosphatase 0.5 Bodansky units. Studies of material collected from the draining sinus demonstrated no acid-fast bacilli, and routine cultures plus cultures for fungi were negative. No bile could be demonstrated in this material.

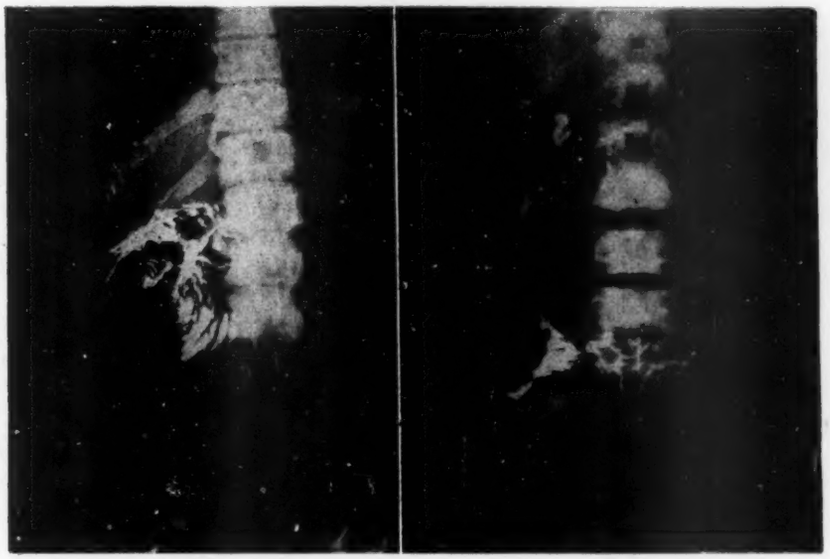

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FIG. 1. (May 30, 1950.) Injection of the sinus tract in the right flank, demonstrating communication with the duodenum which is partially outlined by the contrast material.

FIG. 2. August 23, 1951. Injection of the cutaneous sinus opening in the scar in the right flank, outlining multiple tracts extending along the right paravertebral gutter down to the level of the sacrum. Marked sclerosis of the bodies of the first, third, fourth and fifth lumbar vertebrae is also noted.

Plain x-ray films of the abdomen showed marked sclerosis of the bodies of the first, third, fourth and fifth lumbar vertebrae. (Fig. 2.) The psoas shadows were not visible and the kidney outline could not be seen. A catheter inserted into the sinus tract was seen fluoroscopically to pass along the right lumbar gutter to the level of the spine just anterior to the first lumbar vertebra. Injection of diodrast® failed to show a communication with the bowel. A sinus tract in the right upper quadrant of the abdomen extended inferiorly along the right paravertebral gutter to the level of the sacrum where it crossed to the left side. (Fig. 2.) A barium enema demonstrated a normal colon, and an intravenous pyelogram demonstrated good visualization of the renal calyces, pelvis and bladder. However, on the right there was either malrotation or a tumor mass of the inferior pole of the right kidney with displacement of the ureter laterally.

An upper gastrointestinal series (Fig. 3) demonstrated the duodenal bulb to be markedly deformed on its posterior and inferior surface with a filling defect, ragged in outline, suggesting ulceration. There was a blind pouch which left a "barium stain" suggesting a leak about the area previously visualized by diodrast injection into the fistulous tract. There was some narrowing of the duodenum distal to this portion but the remainder of the duodenum did not appear to be obstructed. A second injection of the fistulous tract with lipiodol again failed to demonstrate a communication with the duodenum.

On August 28, 1951, the previous right flank incision was entered after first placing, under fluoroscopy, a catheter leading up to the first lumbar vertebra. Dissection proceeded along the catheter and it was found that the sinus tract passed through the upper portion of the right kidney, which was surrounded by a markedly thickened capsule. A second sinus tract was found to pass through the lower pole of the kidney. A right nephrectomy was therefore performed and the several sinus tracts were excised. One of the sinuses was found to penetrate the posterolateral duodenal wall just distal to the ampulla of Vater. The duodenal opening was enlarged and the scarred duodenal wall around the sinus tract was excised. The ampulla of Vater was visualized and careful closure of the duodenum with interrupted silk sutures was carried out. Several drains were

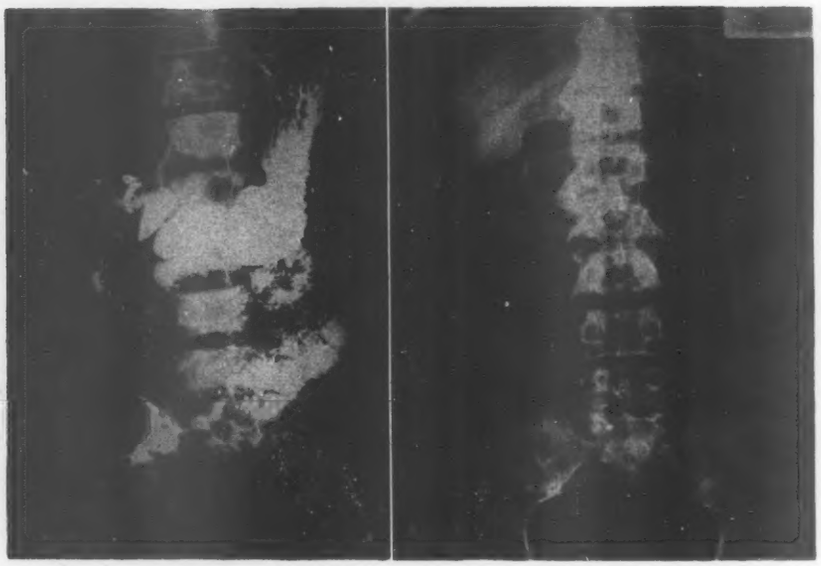

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FIG. 3. (August 23, 1951.) An upper gastrointestinal series demonstrated deformity of the duodenal bulb and a barium-filled pouch suggesting a possible duodenal leak; however, definite communication with the previously outlined sinus tracts could not be demonstrated.

FIG. 4. (September 16, 1951.) Except for changes of chronic osteoarthritis, there was complete return to normal of the lumbar spine following elimination of the fistulas. The marked osteosclerosis of the lumbar vertebral bodies has completely resolved.

placed in the region of the excised sinus tracts and the wound was closed with catgut.

All drains were removed forty-eight hours after the operation and the wound healed primarily. The patient was discharged two weeks later with some diminution in his back pain and with a much improved appetite. When seen three months following operation the patient had gained approximately 30 pounds and was entirely without back pain. No further draining sinuses had developed.

The patient was lost to follow-up until August, 1955, at which time he was found on complete examination to be entirely symptom-free from the time of his operation. His weight had returned to normal and he was fully employed. Further x-ray studies at this time showed a remarkable regression of the degree of sclerosis of the bodies of the lumbar vertebrae as compared with the films taken four years previously. Although there was some residual degenerative arthritic changes, the spine was otherwise normal. (Fig. 4.)

COMMENTS

Renal surgery accounts for 18 to 20 per cent of a reported series of duodenal fistulas [3]. Spontaneous renovisceral fistulas in general are not uncommon, but only seventeen cases involving the duodenum have been reported [*4,5*]. Nearly all cases have been due to a primary renal disease process such as tuberculosis, chronic pyelonephritis, renal calculi and hydatid cyst. In addition, Capon and Wells [*6*] reported a fistula resulting from a hairpin which had perforated the duodenal wall into the right renal pelvis. Stock [*7*] reported the first case secondary to a perforated duodenal ulcer which was treated with nephrectomy and closure of the duodenal fistula. Only five survivals from renoduodenal fistula have been reported, and in one of these there was only a very small fistula for which no surgery was performed [*5*].

The etiology of the case being reported is uncertain, but it is probable that the initial event was a perinephric abscess and that the fistula developed secondary to perirenal disease rather than to operative trauma. The changes in the duodenum noted on x-ray are not inconsistent with the changes of primary duodenal ulcer, and a presumptive diagnosis of perforated ulcer was considered at an earlier operation. However, the patient had no antecedent

history of such disease and there has been no subsequent ulcer problem, although he has in some measure been protected from this by gastroenterostomy. We consider this an example of spontaneous renoduodenal fistula. His initial symptoms were typical of a perinephric abscess and, as has been noted in the literature, virtually all spontaneous renoduodenal fistulas have originated in renal rather than duodenal disease.

The choice of management of renoduodenal fistulas depends on the size of the fistula and the rate of loss of duodenal contents. Colp [*8*] believed that conservative measures would usually suffice and spontaneous closure would follow [*5*]. When this fails to occur, primary excision and closure of the duodenal fistula, usually in association with nephrectomy when this has not already been accomplished, is recommended for the treatment of chronic established fistulas in patients in adequate nutritional balance [*9–12*].

The roentgenologic changes of sclerosis of the lumbar vertebrae present an interesting associated finding in this case especially as these changes were reversible, being absent in the follow-up x-ray (Fig. 4) taken four years later. The pathophysiology of this sclerosis is obscure but would appear to be related in some way to the adjacent sinus tracts associated with the renoduodenal fistula. We are unable to find any report of similar radiologic changes in the literature.

SUMMARY

A case is presented of a long-standing chronic and debilitating renoduodenocutaneous fistula which responded favorably to direct surgical excision and closure of the fistula after two previous surgical approaches had failed.

The incidence, etiology and therapy of spontaneous renoduodenal fistula is briefly considered in relation to the case presented.

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Spondylolysis and Trauma

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DEFECTS of the pars interarticularis usually occur in the lumbar spine and most frequently in the fifth neural arch. When back pain is present in these cases, it may be accompanied with pain, paresthesia, numbness, weakness or reflex changes in one or both lower extremities.

The problems yet unsolved concerning this lesion are its etiology and surgical treatment. The accepted theory has been that this condition is of congenital or developmental origin although there is doubt from an embryological viewpoint. Experimental work to disprove the developmental idea has been inconclusive.

Supportive evidence of traumatic etiology has been obtained from x-ray statistics which show a higher percentage of spondylolysis in adults than in children. In Eskimos and in certain occupations where back bending is involved, an unusually high rate of occurrence is also found. Thus there is presumptive evidence that trauma is a definite factor in spondylolysis.

A case is presented which indicates that trauma may also produce symptoms in a defective lumbar pars interarticularis.

CASE REPORT

A thirty year old woman employed as a solderer had had no difficulty with her back until August 20, 1955, when she was struck in the back by an automobile. Because of severe low back pain which followed this accident, she consulted a doctor who had her catheterized and administered diathermy to the back. Urinary frequency developed and she was sent to a urologist for cystoscopy and pyelography. A defect in the third lumbar neural arch was noted by a radiologist, who made the diagnosis of a congenital cleft defect. She complained of low back pain radiating down the left thigh which was also paresthetic. Physical activity aggravated, and rest relieved, the condition. Examination revealed left paralumbar muscle spasm, percussion tenderness over the third lumbar vertebra to the left of the midline, and pain on lumbar extension and left lateral bending. X-ray films showed a defect of the left pars interarticularis of the third lumbar vertebra, with apparent increase in bone formation superior to the cleft. (Figs. 1 and 2.)

Treatment advised was laminectomy without fusion, and this was carried out on October 11, 1955. The day following surgery there was complete absence of pain in the lower extremity and paresthesia. The patient walked four days postoperatively and was discharged on the seventh day with no complaints in the back or the legs.

The material was submitted to the Armed Forces Institute of Pathology for histological study. The report received stated that along one margin of the fibrocartilage there was a bulge where the older fibrocartilage had been damaged and some repair was present. This defect was an anomalous synchondrosis which formed a point where an injury that otherwise would have produced no anatomic disturbance could produce a disturbance and its attendant backache. Histologically, there was dense, opaque, mature cortical bone at the sides joined to each other by a band-like central area of less dense and somewhat immature, more faintly stained bone. The sites of transition were irregular and jagged in places, and somewhat basophilic. (Figs. 3 and 4.)

COMMENT

This case of spondylolysis is presented because of its unusual site, histological evidence of trauma in a defective structure, and rapid

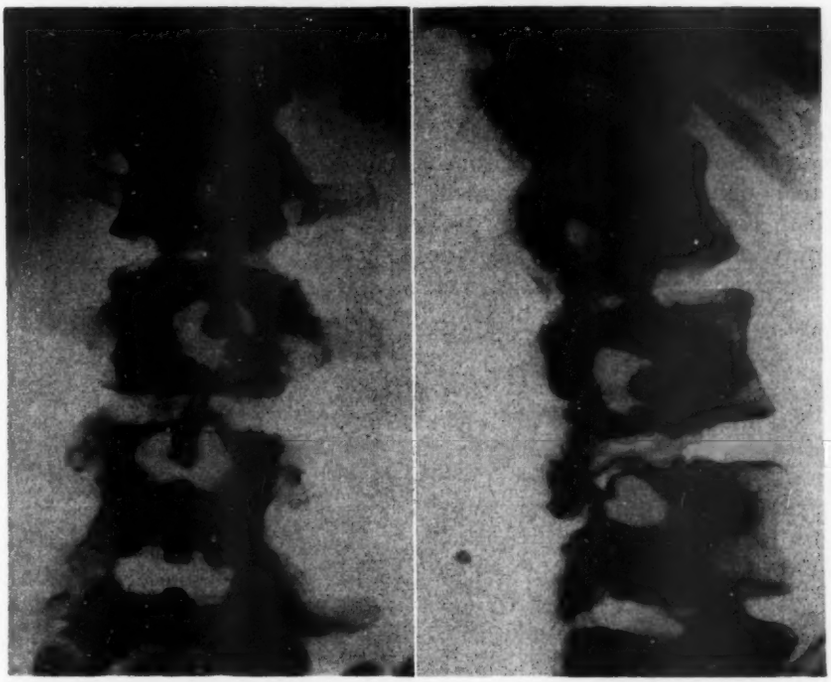

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FIG. 1. Anteroposterior view of the lumbar spine shows a cleft defect of the third lumbar left lamina.

FIG. 2. Oblique view of the lumbar spine demonstrates the spondylolysis.

FIG. 3. Normal bone is firmly attached to fibrocartilage.

FIG. 4. Irregular and jagged transition of the fibrocartilage at its attachment to bone, indicative of posttraumatic repair.

relief of pain following simple laminectomy without fusion.

SUMMARY

1. Spondylolysis can occur unilaterally in the lumbar spine and exist without symptoms.

2. Trauma to a defective pars interarticularis may result in symptoms.

3. Laminectomy without fusion may provide rapid and complete relief from back pain.

Acknowledgment: We wish to thank Dr. Lent C. Johnson of the Armed Forces Institute of Pathology, Washington, D. C., and Dr. Martin Swerdlow of Menorah Hospital, Kansas City, Missouri, for their interpretations of the histological sections.

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The Danger from Thorotrast As a Medium for Intracranial Angiography

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Thorotrast is a radioactive colloidal solution of thorium dioxide. Thorium emits alpha, beta and gamma rays, and has a half-life of 1.4 by 10^{10} years. The intensity of the beta and gamma radiation from this material is very slight. However, in samples of 25 cc., thorotrast is said to emit alpha particles within minimum-maximum limits equivalent to 0.5 to 1.0 μg. of radium.

Thorotrast is ideal for intracranial angiography because it is water-miscible, highly opaque to x-rays and virtually non-irritating. However, after being injected it is excreted very slowly, most of it being retained in the reticuloendothelial system. (Fig. 1.)

Intracranial angiography is often done using the pericutaneous method with the possibility of extravasation into the surrounding tissue.

The case reported herein illustrates a granulomatous and fibrous reaction (Figs. 2 and 3) occurring after accidental extravascular injection of thorotrast. These changes could conceivably be due to a combination of radiation effect and local inflammatory reaction.

CASE REPORT

The patient, a twenty-three year old woman, was well until June 5, 1945, when she suddenly experienced severe frontal headache. Shortly

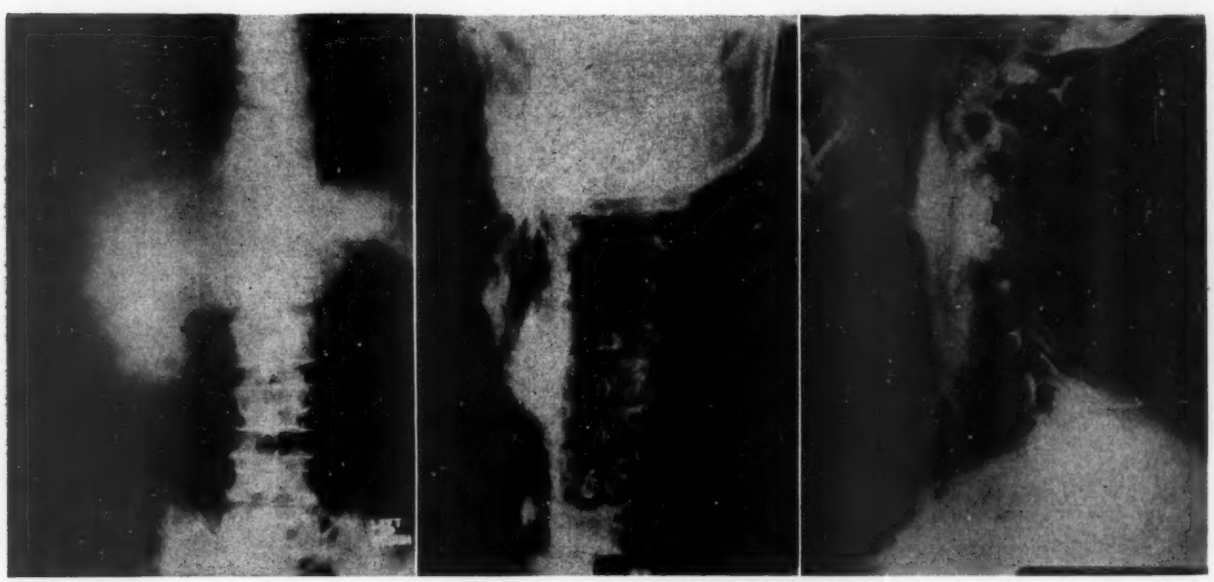

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Fig. 1. Opacification of liver following injection of thorotrast intravenously.

Figs. 2 and 3. Thorotrast deposited in cervical area following extravascular injection.

thereafter she became paralyzed on the right side and aphasic. She began to vomit repeatedly during the next day. Speech began to return on June 9th but she remained paralyzed and incontinent. There was no history of hypertension.

Physical examination on admission, June 10th, showed right hemiparesis and hyperreflexia, right central facial weakness, bilateral papilledema of several diopters and urinary retention with overflow.

Laboratory studies revealed the following: hemoglobin, 93 per cent; white blood cell count, 12,000 per cu. mm., with a normal differential; blood urea nitrogen, 17 mg. per cent. Urinalysis was negative. Blood Kolmer and Kline tests were negative. Spinal fluid was xanthochromic; water pressure, 240 mm.; protein, 60 mg. per cent. Serology was negative and the colloidal mastic test was normal.

An arteriogram was made on July 7th and showed poor filling of the left anterior and middle cerebral arteries, suggesting a lesion near the juncture of the anterior cerebral and carotid.

The electroencephalogram was unsatisfactory. X-ray films of the chest and skull were negative for any abnormalities.

The patient's hospital course was one of fairly rapid improvement. She regained bladder control after several weeks, the aphasia disappeared, and she regained considerable power in the right arm and slight return of function of the right leg. Papilledema seemed to recede somewhat and she was discharged on July 22nd in the care of her family physician. The patient and her husband were given instructions for carrying out physiotherapy including massage, active and passive motion, and baking at home

The diagnosis was: cerebrovascular accident; probable rupture of congenital aneurysm in the left frontal lobe.

On July 16, 1956, the patient's condition had improved except for a dragging limp of the left leg. However, hoarseness had developed three to four months previously. Physical examination revealed a stony hard mass in the left side of the neck. Mirror laryngoscopy showed complete vocal cord paralysis on the left, with resultant overhang of relaxed arytenoid eminence. There was no tumor of the larynx. The laryngeal paralysis was due to pressure on the left recurrent nerve by the hard mass caused by thorotrast infiltration.

SUMMARY

Thorotrast, although ideally suited for intracranial angiography, should not be used because by experimental work it is known to be carcinogenic and can cause severe granulomatous and fibrotic reaction when extravasated into soft tissue.

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Submucous Lipoma of the Colon

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LIPOMAS of the colon are surgically important because they are difficult to differentiate from carcinoma. The confusion is understandable, but should be resolved at the operating table when proper recognition will allow local excision rather than extensive colonic resection.

These lesions are not as rare as formerly believed. They are the second most common benign tumor of the colon, being exceeded in incidence only by adenomatous polyps. They may occur throughout the gastrointestinal tract but are most frequent in the colon where two types are found, the submucous and the subserous [1]. The subserous tumors usually arise from the appendices epiploicae. They comprise 10 per cent of colonic lipomas and will not be considered in this discussion.

Submucous lipomas include 90 per cent of the total and may vary in size from a small accumulation of lipoid cells to a tumor the size of an orange. Most of them arise under the mucosa at the mesenteric border and may be sessile or pedunculated. When pedunculated they may have a long pedicle and ride up and down within the colon with peristaltic activity. They may twist on their pedicle, with necrosis and separation. About twenty such lipomas have been described as having been passed spontaneously, the first being reported by Bower in 1757 [2].

These tumors occur somewhat more frequently in females and the average age is about fifty. A large number of them produce no symptoms and are found at necropsy or as an incidental finding at surgery. Those that produce symptoms follow no definite pattern and may be of an obscure nature for many years. In one reported case the patient had had episodes of abdominal pain and constipation for fifteen years prior to surgery [3].

In general, symptoms may be produced by obstruction, intussusception or bleeding. Obstruction is rarely complete since, unlike carcinoma, the wall of the colon is not infiltrated and contracted but retains its normal elasticity permitting the passage of intestinal contents past the tumor. For this same reason, intussusception is a common finding in lipoma of the colon. There may be recurrent bouts of

FIG. 1. X-ray film of colon showing a large polypoid mass in the ascending colon.

FIG. 2. Tumor mass showing ulceration of mucosa at apex.

FIG. 3. Cut section of tumor mass.

cramp-like pain, nausea and constipation for many years. Other findings include diarrhea, hemorrhage, anemia and palpable tumor. Hemorrhage is due to erosion of the mucosa over the apex of the tumor. A survey of presenting symptoms has produced the following distribution: pain, 75.2 per cent; palpable tumor, 74.2 per cent; constipation, 54.4 per cent; weight loss, 14.6 per cent; bleeding to the extent of anemia, 7.9 per cent [5].

X-ray examination of the colon usually brings forth a report of either obstructing lesion, filling defect or polypoid mass with or without tendency toward intussusception. The most common diagnosis is "filling defect compatible with carcinoma."

Treatment should be colotomy and local excision of the tumor. Those with long pedicles may be tied off and removed. The sessile type can be enucleated with a portion of the mucosa which frequently is ulcerated. However, since it is difficult to make a differential diagnosis from carcinoma of the colon, most cases (60 per cent in one series) have been treated by resection [3].

CASE REPORT

M. C., a fifty year old Negro man, was first seen on June 20, 1956, and hospitalized. He gave a history of intermittent right abdominal pain, cramping in nature, lasting three to four minutes at a time and radiating to the right groin. This had been present for one year but had never occurred at night. He found relief by lying on his right side. There was no melena, diarrhea or constipation. His appetite was good. There had been a weight loss of 5 pounds over the last few weeks. The pain became persistent on the day of admission but subsided twenty-four hours later. Physical examination revealed tenderness on deep pressure in the right lower quadrant of the abdomen. The stool was positive for occult blood on two occasions. A heavy infestation with strongyloides was repeatedly demonstrated.

Colonic x-ray films taken on June 25th and repeated on June 29th revealed a large polypoid mass in the ascending colon "compatible with carcinoma." (Fig. 1.)

The patient was given gentian violet for the strongyloides and was prepared for colonic surgery with neomycin.® On July 5th, through a right paramedian incision, the right side of the colon was exposed, and on palpation of the colon a rubbery mass about the size of a golf ball was felt in the ascending colon several inches below the hepatic flexure. The serosa was not involved, there was no puckering and, with the exception of the mass, the colon appeared to be grossly normal. From these findings it was strongly suspected that the lesion might be a lipoma of the colon, and therefore a colotomy was performed revealing a round submucosal mass arising from the mesenteric border. The overlying mucosa was intact with the exception of a small area at the apex which was ulcerated. (Fig. 2.) A circumscribing incision was made through the mucosa and a soft tumor mass was easily enucleated. (Fig. 3.) The posterior mucosal wall and the colotomy incision were closed. On July 9th the patient showed evidence of atelectasis

of the right lower lobe. The next day he was intubated and a mucous plug was removed. That afternoon he had a wound dehiscence and was taken to surgery and it was closed with wire. He continued to have symptoms of a pulmonary infection and was treated with antibiotics, potassium iodide and steam inhalation. He gradually improved, sutures were removed on July 21st and he was discharged on July 23rd.

COMMENTS

This patient presented a recurrent low grade obstruction of the bowel with x-ray evidence of a mass in the ascending colon. Examination of stools revealed the presence of a strong infestation with strongyloides.

Examination of the literature did not indicate any evidence of strongyloides producing a granulomatous lesion of the colon. Because of this, exploration was performed after preparation with gentian violet to avoid the possibility of dissemination of the parasites. At surgery the lesion was recognized and simple enucleation performed. The postoperative complications, while significant, were less serious because the patient had not been subjected to an extensive surgical procedure.

SUMMARY

1. A case of lipoma of the colon is presented in a patient who also had a parasitic infection with strongyloides.

2. At surgery the nature of the lesion was recognized and simple enucleation performed.

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Neurofibroma of the Rectum in a Patient with von Recklinghausen's Disease

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THE visceral manifestations of disseminated neurofibromatosis (von Recklinghausen's disease) have been mentioned in the medical literature [*1,2,4,5,12*]. Lesions comparable to those seen in the skin are sometimes found in the central nervous system, bones and occasionally in the gastrointestinal tract. Neurofibroma of the rectum is extremely rare and can be the manifestation of generalized neurofibromatosis, or may even appear as a solitary tumor [*1,3,7,12*]. In several recent comprehensive reviews of submucosal and other rectal tumors, cases of neurofibroma were not listed [*9,10*]. Sarcomatous transformations have not been mentioned in the few reported cases of rectal lesions. However, neurofibroma should always be considered in the clinical differential diagnosis of submucosal rectal nodules. These will include oleoma, lymphoma, lipoma, fibroma, leiomyoma, carcinoids, and their malignant sequelae [*10*].

Generalized neurofibromatosis of the skin was first described by von Recklinghausen in 1882. Subsequent observations have shown that the widespread anomalous tumors of the skin and the associated "café au lait" macular changes are definitely characterized by an origin early in life and dormancy or slow progression of the tumors. Noteworthy, also, are the evidences of a heredo-familial background, the frequent presence of mental retardation and occasional involvement of the bones and central nervous system. Malignant transformations have been reported in lesions of the skin, gastrointestinal tract, bones and nerves [*6,11*].

The lesions, whether dermal or submucosal, are usually elevated, circumscribed, nonindurated and painless. The histologic origin of the tumor is assumed to be neuroectodermal. The chief source of the tumors are the schwannian sheath cells, although a few writers still favor a mesodermal, connective tissue, neural derivation [*8*]. Auerbach's myenteric nerve plexus is unquestionably the source of the submucosal, rectal and colonic lesions [*12*]. The tumors are composed basically of fibrous connective tissue and contain varying amounts of loose and wavy intercellular collagen bundles, with scattered, parallel oval or spindle-shaped nuclei. A few non-medullated nerve fibrils often may be demonstrated by Bodian's silver protein stain [*8*]. Masson's trichrome and phosphotungstic acid hematoxylin stains will effectively demonstrate the collagen bundles.

Clinically, the rectal tumor is usually asymptomatic, single, soft and impalpable, and is discovered during proctoscopy. The mucosal covering is invariably unchanged and the diagnosis will be made only by microscopic examination of the lesion. Excision of these tumors may be necessary if there is impairment in body function due to the size, number or position of the lesions [*3,7,12*].

I recently had the opportunity of observing a female patient with long-standing disseminated neurofibromatosis of the skin. She was referred for proctologic consultation because of unexplained anemia and the presence of occult blood in the stools. There were no symptoms directly referable to the rectum or colon. On proctosigmoidoscopic examination a small, benign adenomatous polyp and an anterior submucosal rectal tumor were found. The exact nature of the anterior nodule was determined only after microscopic examination.

FIG. 1. Microscopic section of the rectal tumor. Note the intact mucosa and the wavy collagen tissue bundles of the submucosa in the random arrangement characteristic of neurofibroma. Hematoxylin and eosin, original magnification × 100.

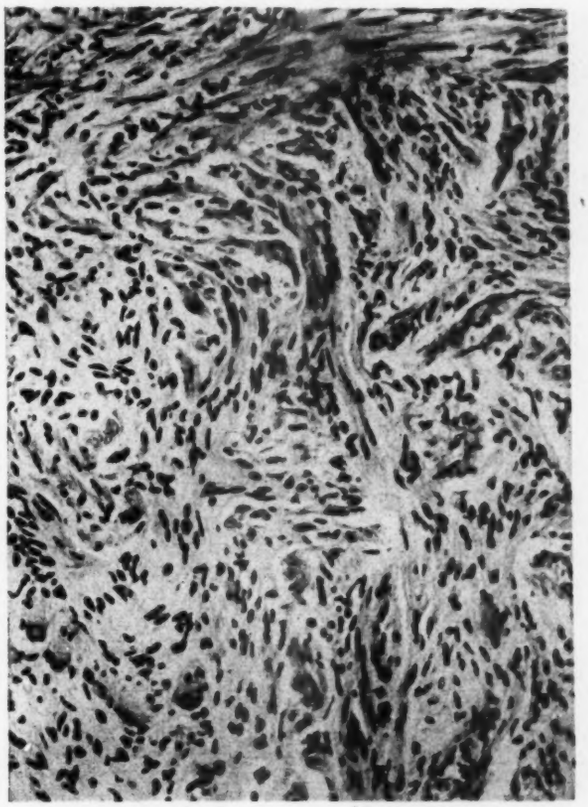

FIG. 2. Central portion of the rectal tumor. Note the wavy collagen fibrils and the interspersed oval or spindle-shaped nuclei. A few ganglion cells and muscle fibers are also present. Hematoxylin and eosin, original magnification × 250.

CASE REPORT

A seventy-eight year old white woman entered Mt. Zion Hospital in January, 1957, because of the sudden development of a non-reducible femoral hernia. Laboratory studies revealed a hemoglobin of 10 gm. per cent and occult blood in the stools. A gastrointestinal series gave negative results and colonic studies showed sigmoidal diverticula. The patient had a previous history of treated syphilis and the Wassermann test was 2 plus. Roentgenologic studies of the pelvis demonstrated pagetoid changes in the bones. Multiple, scattered, nonprogressive neurofibromatous nodules of the skin and associated café au lait spots, mostly on the trunk, had been present since childhood. The patient was somewhat mentally retarded. A hemorrhoidectomy had been performed some years previously.

A proctologic consultation was requested. The examination revealed a 1 cm. pedunculated adenomatous polyp on the posterior rectal wall at the 14 cm. level, and a prominent, previously impalpable nodule on the anterior rectal wall at the 8 to 10 cm. level. The tumor was 2 cm. in diameter and was non-indurated, covered by unchanged mucosa and slightly mammillated. The adenomatous polyp was excised by electrosurgery and specimens for biopsy were taken from the anterior submucosal nodule.

Pathologic examination revealed that the excised polyp was benign. The biopsied sections of the anterior submucosal tumor were treated with hematoxylin and eosin, phosphotungstic acid hematoxylin and Masson's stains. The tumor consisted mainly of loose, wavy collagen tissue bundles arranged in a rather random fashion. Scattered oval and spindle-shaped nuclei were interspersed among the fibrils of connective tissue. A few ganglion cells and muscle fibers were also present. The mucosal surface appeared entirely normal. The diagnosis was neurofibroma of the rectum. (Figs. 1 and 2.)

A herniotomy was performed but removal of the rectal neurofibroma was deferred. However, there will be continued observation of the benign rectal tumor.

SUMMARY AND CONCLUSIONS

A case is presented of an elderly woman with disseminated neurofibromatosis of the skin and a similar lesion in the rectal wall.

Neurofibroma of the rectum is an unusual submucosal lesion which may occur as an independent nodule or in the course of generalized von Recklinghausen's disease.

A rectal neurofibroma is generally asymptomatic, single and impalpable. It is usually covered by normal mucosa and can be diagnosed accurately only after microscopic examination. The lesion is clinically significant in the course of a differential diagnosis of submucosal and other rectal tumors.

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Leiomyosarcoma of the Stomach

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LEIOMYOSARCOMA of the stomach is a rare condition but responds unusually well to early diagnosis and surgical removal.

Ninety-four cases of leiomyosarcoma have been reported in the literature and the incidence is one leiomyosarcoma in every 1,000 cases of gastric malignancy.

Golden and Stout [1] reported twenty-one of the aforementioned cases. It was their belief that these tumors practically never show the invasive or metastatic characteristics of the typical sarcoma.

PATHOLOGY

Grossly the leiomyosarcoma is a soft tumor which originates in the muscularis of the stomach; it does not spread laterally but progresses towards the lumen in the endogastric or submucosal type or towards the serosa in the exogastric or subserosal type. The center usually breaks down and ulcerates, which accounts for the bleeding and anemia. Microscopically there are usually many atypical, short cells and irregular forms with poor organization and mitotic figures. Two or more mitotic figures per high power field labels the tumor as a malignant leiomyoma.

SIGNS AND SYMPTOMS

The symptoms of leiomyosarcoma are usually those of gastric ulcer, and if the tumor is a submucosal type hemorrhage will occur sooner or later. Therefore, hematemesis or melena with resulting anemia is the usual course and the presenting signs when first seen.

Since this is an unusual lesion which responds well to early diagnosis and surgery, the following case report is added to the literature.

CASE REPORT

H. C. H. (No. 46 926) was admitted to the hospital on January 21, 1956, with a chief complaint of weakness, nervousness and easy fatiguability. His other symptoms consisted of dyspnea on exertion and dizzy spells with an attack of syncope one week prior to admission. He was known to have hypertension for five years. There was an episode of rectal bleeding which occurred two years prior to admission and intermittently since then, but was never severe.

Physical examination revealed a well developed, somewhat obese sixty year old white man who did not appear to be acutely or chronically ill. Blood pressure was 142/106 mm. Hg. The eye grounds showed a slight tortuosity of the retinal vessels with some AV compression. The liver was palpable and tender.

Laboratory examinations revealed hemoglobin 15 gm. per cent and a white blood cell count of 13,450 per cu. mm. The urinalysis showed many white blood cells. The non-protein nitrogen was 35 mg. per cent and blood serology was negative. X-ray of the chest on January 23, 1956, was reported as "No pathology."

Gastrointestinal x-ray series on February 16, 1956, revealed a sharply defined semi-circular defect on the anterior wall of the lower portion of the body of the stomach near the greater curvature. This defect was visualized only in the right oblique reclining position. However, it was demonstrated sufficiently to prove that it represented a definite lesion. It measured 5 cm. across its base and 2 cm. in height. It was interpreted as lying submucosally. (Fig. 1.)

An electrocardiogram taken on January 24, 1956, read "Abnormal tracing with T-wave inversion in many leads suggestive of myocardial ischemia."

The patient's early course in the hospital consisted of symptomatic treatment, sedation and digitalization. A proctosigmoidoscopic examination revealed hemorrhoids to be the source of his rectal bleeding.

FIG. 1. Leiomyosarcoma of the stomach. Diagnosis based on gross and microscopic examination.

FIG. 2. Gross examination: The fresh specimen consists of a segment of stomach measuring 6 cm. along the lesser curvature and 11 cm. along the greater curvature. On the greater curvature, there is a tumor mass measuring 4 cm. in diameter which is submucosal in location. The tumor protrudes through the serosa but does not ulcerate the serosa at any point. The musculature in the area appears destroyed. The tumor is a yellowish white with small hemorrhagic areas, and very firm. It appears completely removed.

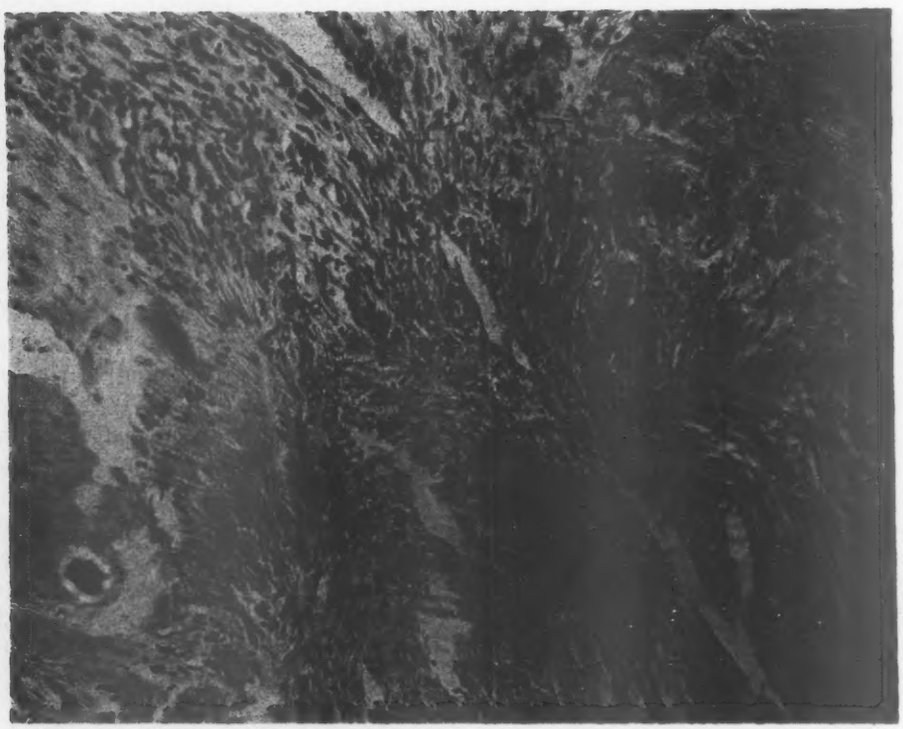

FIG. 3. Microscopic examination: The mucosa is intact over the tumor. Within the submucosa and destroying the musculature in the region, there is a mass composed of spindle cells which in most areas are quite well differentiated and show no mitotic activity; however, around the periphery of the tumor the cells become more anaplastic, and mitotic figures are noted. There are also giant cells. The tumor is definitely invading the surrounding musculature. No lymph node or vascular involvement is noted.

A gastroscopic examination performed on February 24, 1956, showed a 1.5 cm. area of grey, necrotic mucosa with an ulcerated pit in the center, located on the anterior wall of the lower portion of the body of the stomach near the greater curvature.

The patient was told of the additional hazard of surgery as manifested by the electrocardiographic findings of myocardial infarction. He consented to surgery, however, and a laparotomy was performed on March 8, 1956. The stomach presented a tumor on its greater curvature about 4 cm. in diameter and approximately 8 cm. proximal to the pyloric ring. (Fig. 2.) The lesion was circumscribed and there was no evidence of metastasis to preaortic or other lymph nodes. In view of the patient's cardiac status, a sleeve resection of the stomach was performed. The pathological examination of the tumor was reported as leiomyosarcoma. (Fig. 3).

The patient's postoperative course was somewhat stormy. Pulmonary edema developed immediately postoperatively which necessitated a temporary tracheotomy. This was thought to be due to cardiac decompensation. The patient experienced much coughing following this. A partial wound separation occurred on the fifteenth postoperative day which required suturing. His course then continued satisfactorily.

This patient returned to the hospital on May 23, 1956, for follow-up examination. He was symptom-free and his weight had returned to normal. His blood pressure was 140/100 mm. Hg.

He was instructed to return every six months for a check-up.

SUMMARY

1. A case of leiomyosarcoma of the stomach is presented.

2. This case is atypical and represents the asymptomatic type without gastrointestinal bleeding or other symptoms referable to the stomach. The diagnosis was suggested by a routine gastrointestinal series and gastroscopic examination, and later proved at surgery.

3. This is a rare tumor with a good prognosis.

Acknowledgment: The technical assistance of Mr. John Templeton from the Illustration Laboratory, V. A. Hospital, Montgomery, Alabama, in supplying the radiographs and photomicrographs is gratefully acknowledged.

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Malignant Ovarian Tumor with Ascites and Hydrothorax Simulating Meigs' Syndrome

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THE triad of ovarian fibroma, ascites and hydrothorax as described by Meigs and Cass [1] in 1937 has re-emphasized the significance of this uncommon but highly important syndrome. It is of historical interest that a number of authors, principally Demons, Cullingworth and Spiegelberg, had previously described the occurrence of pleural and peritoneal cavity fluid with ovarian tumors. It remained for Meigs and Cass, however, to demonstrate the importance of surgical exploration in all suspected cases and consequently, this syndrome has been named in honor of the senior author.

Much emphasis has been given Meigs' syndrome in the literature during the past twenty years and consequently, it is becoming increasingly common to find this syndrome included in the differential diagnosis of female patients with pleural effusion and ascites. In the face of this awareness, there remain an appreciable number of women who are denied the chance for an early and complete cure by failure to appreciate this syndrome. Beresford [2] has noted that these patients are frequently assigned to medical wards with such diagnosis as cirrhosis of the liver or congestive heart failure. Perhaps, just as often, they are considered as having a malignant ovarian tumor with metastases and are given up as hopeless.

In recent years, Meigs [3] has stated that only those tumors which are solid, benign and "fibroma-like" should be included in this syndrome. Thecomas and granulosa cell tumors are fibroma-like and for this reason have been included. Unfortunately, for purposes of classification a certain number of the latter are, in fact, malignant and therefore the concept of benignity as a prerequisite for inclusion needs revision. Kimbrough [4] has stated that the syndrome should include either ovarian fibromas only, or else all ovarian tumors both cystic and solid with ascites and hydrothorax provided there is no evidence of metastasis in the peritoneal and pleural cavities.

Inasmuch as the importance of recognition of the syndrome is in its therapeutic implications rather than in uncovering medical curiosities, we are in agreement with the last proposal. If this were to become generally accepted, all patients with adnexal masses associated with the other two features of the syndrome would be considered in this category and additional patients might be salvaged. The following case report is an example of this situation.

CASE REPORT

H. Y., a fifty-five year old white female schoolteacher, unmarried, was admitted with the complaint of a 20 pound weight loss accompanied by an enlarging abdominal mass in the lower portion of the abdomen. These symptoms were noted to develop during the twelve months prior to admission. The menopause was uneventful and there had been no vaginal bleeding for two years. The patient denied having pain in the abdomen and attributed her weight loss to dieting over the past year. Family history revealed that the patient's mother underwent a mastectomy for cancer of the breast twenty-four years ago and was presently living and well. The past history was noncontributory. On physical examination, the temperature w 98.4°F; pulse 100 and blood pressure 130/70 mm. Hg. The patient was 67 inches tall, weighed 135 pounds and was a well developed, well nourished white woman with no apparent evidence of weight loss. Head and neck were negative for significant abnormalities. Auscultation of the chest revealed a dull friction rub at the left base anteriorly; the remainder of the lung fields were clear.

Palpation of the abdomen showed a large mass in the left lower quadrant which extended above the umbilicus. It was bulbous and appeared cystic. On pelvic examination a movable non-tender cervix with a slight bluish hue was seen and the uterus was small and markedly anteflexed. The mass appeared to be continuous with the left adnexa. The right adnexal area appeared normal. There was no peripheral edema noted. The remainder of the examination was essentially within normal limits.

Laboratory studies revealed a hemoglobin of 14.6 gm. and 4.5 million red blood cells per cu. mm. Urinalysis was completely within normal limits and the serology as determined by the VDRL method was negative. X-ray of the chest showed a pleural effusion on the left side. (Fig. 1.)

FIG. 1. Roentgenogram of the chest showing left hydrothorax.

Shortly after admission, thoracentesis was performed and 20 cc. of blood-tinged fluid was aspirated from the left pleural cavity. This fluid was centrifuged and examined microscopically. In addition to red cells, there were numerous small round cells and large histiocytes, but no cells were noted which were thought to be of malignant type. Several days later, the patient was taken to surgery and the pelvis was explored through a midline incision. Considerable ascitic fluid was present and a large cystic tumor was encountered which measured 26 by 18 by 13 cm. and weighed 3,600 gm. The tumor was attached to the left fallopian tube and uterus and had the appearance of a cystadenocarcinoma of the ovary. Total hysterectomy with bilateral salpingo-oophorectomy was carried out without difficulty. The peritoneal cavity was explored for evidence of metastatic seeding, but no abnormalities were noted. The abdomen was closed and the patient was returned to her room in good condition. Postoperatively the course was uncomplicated. The patient was discharged from the hospital on her ninth postoperative day and re-examination at varying intervals over the past twelve months revealed no evidence of recurrence. She is presently back at her work teaching school; she has gained 15 pounds and looks and feels well. Repeated x-rays of the chest reveal complete resolution of the previously noted left pleural effusion. The patient has no pulmonary symptoms.

Figure 2 shows the specimen opened and reveals the numerous cystic cavities within the tumor mass. The cysts contained a dark serosanguineous fluid and in some areas, dark yellowish purulent exudate was present. The tumor tissue was yellowish gray and the cysts were lined with small papillary tumor projections. Histopathologically, a typical papillary serous cystadenocarcinoma was found. (Fig. 3.)

COMMENTS

It is interesting to note that a variety of cystic and solid lesions may produce ascites and hydrothorax. In addition to the ovarian neoplasms [*5,8–10*], there are leiomyomas of the uterus, fallopian tube papillomas, adenocarcinomas of the uterus, and cystic and neoplastic lesions of the pancreas. In the majority of patients the pleural effusion is limited to the right side, but it is not too uncommon to be left-sided or even bilateral.

Many theories have been suggested to explain the unusual formation of ascitic and pleural fluid. Those more commonly mentioned include edema of the tumor, pressure on abdominal lymph channels and the presence of a hypersensitivity state (Selye's alarm reaction). None of these theories have been entirely satisfactory in that certain aspects are not always adequately explained.

It has been shown that the fluid migrates from the abdominal cavity to the chest in most

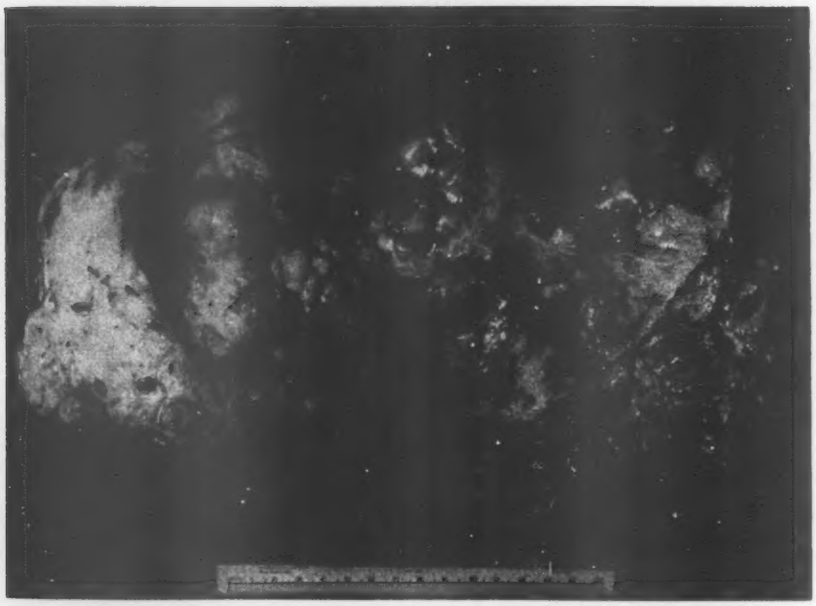

FIG. 2. Gross appearance of the tumor mass sectioned through its mid-portion.

FIG. 3. Photomicrograph of the tumor showing a papillary serous cystadenocarcinoma.

instances. However, it should be remembered that a small fibroma with little or no ascitic fluid may be associated with hydrothorax of considerable degree. In the case reported by Annest [6,7] a very small fibrous tumor was present with no ascites although there was a marked hydrothorax. Following oophorectomy, the chest cleared and the patient is well without recurrent pleural effusion five years later.

Meigs in 1953 had reported eighty-four cases of true Meigs' syndrome, and if one considers all other cases such as cystadenocarcinomas, Brenner cell tumors, teratomas and Krukenberg tumors, there would be approximately 200 case reports at this time. The case reported herein demonstrates the salient features of the syndrome and varies from the original definition of the Meigs' syndrome only by the presence of a non-fibrous ovarian tumor.

SUMMARY AND CONCLUSIONS

Meigs' syndrome is a rather uncommon but important condition requiring abdominal exploratory surgery and resection of the ovarian tumor. Many patients previously considered hopeless from a variety of misdiagnosed conditions such as metastatic malignant tumor, congestive heart failure, cirrhosis of the liver, etc., may be given a new lease on life by resection of the ovarian tumor. A case demonstrating the various features of Meigs' syndrome has been presented. The authors are in agreement with the proposal of Kimbrough for the inclusion of all ovarian tumors with associated ascites and hydrothorax providing there is absence of peritoneal or pleural metastases.

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Hematoma of the Duodenum

REPORT OF A SURGICALLY PROVED CASE

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HEMATOMA of the duodenum as a cause of gastrointestinal obstruction is a relatively infrequently reported entity. The case to be reported herein presents a typical pattern and is surgically proved.

CASE REPORT

The patient was a four and a half year old boy who was admitted to the hospital for persistent vomiting of two days' duration associated with vague abdominal pain. At the time of admission the only history which appeared related to the present illness, as given by the parents who were reliable medical observers (a doctor and nurse), was that two weeks prior to admission the patient had had "booster shots." Since that time he had not been entirely well, suffering from a croupy cough with expectoration of mucus. There had never been any previous similar episodes of vomiting.

Except for varicella and occasional upper respiratory infections, the patient had always been well. There were no other positive findings in the past or family histories.

Physical examination revealed a well developed, well nourished white male child of the stated age, in moderate distress and complaining of vague abdominal pain. The patient appeared dehydrated and vomited frequently during the examination. The vomitus was bile stained. The patient's temperature was 99°F. and the pulse rate 100 per minute. The remaining positive physical findings were limited to the abdomen, which was diffusely tender and somewhat rigid with splinting. There was no rebound tenderness or distention. No masses were palpable.

A white blood count on admission was 15,000 cells per cu. mm., 80 per cent of which were polymorphonuclear leukocytes with 4 per cent stab cells. The urine, collected while the patient was receiving a glucose infusion, showed 2 plus glucose and 4 plus acetone.

A clinical diagnosis of intestinal obstruction was made and roentgenological examinations were performed in an attempt to make a more definitive diagnosis.

A survey film of the abdomen showed the presence of an ovoid mass density, 5 cm. in diameter, in the left upper quadrant of the abdomen adjacent to the first two lumbar vertebrae. This mass caused a pressure defect on the greater curvature of the stomach which was the only hollow viscus containing air. The psoas shadows were well defined. An intravenous pyelogram (Fig. 1) showed that this mass was not renal in nature. With a barium swallow (Fig. 2), the aforementioned defect on the greater curvature of the stomach was again demonstrated. The duodenal sweep showed irregularity, widening of the lumen and a coarsening of the mucosal pattern. At no time did any barium proceed beyond the angle of Treitz.

A differential diagnosis of mesenteric cyst, pancreatic cyst, retroperitoneal tumor or hematoma was made.

With the latter possibility in mind, more pointed questioning of the patient and his parents revealed that twelve days prior to admission the child had fallen on a park bench and injured his abdomen. There had been no subsequent complaints referable to this trauma.

Because of the persistent mass density and complete obstruction at the level of the retroperitoneal duodenum surgery was performed forty-eight hours following admission. The patient was prepared with a nasogastric tube and the insertion of an intravenous polyethylene catheter.

Under general anesthesia a left upper transrectus incision was made. A large hematoma was found in the area of the fourth portion of the duodenum extending into the ligament of Treitz, dissecting subserosally along the first loop of jejunum and extending into the transverse mesocolon anterior to the pancreas. There was complete compression

FIG. 1. Demonstration of mass in left part of the abdomen, which was not related to the kidney but caused extrinsic pressure on stomach.

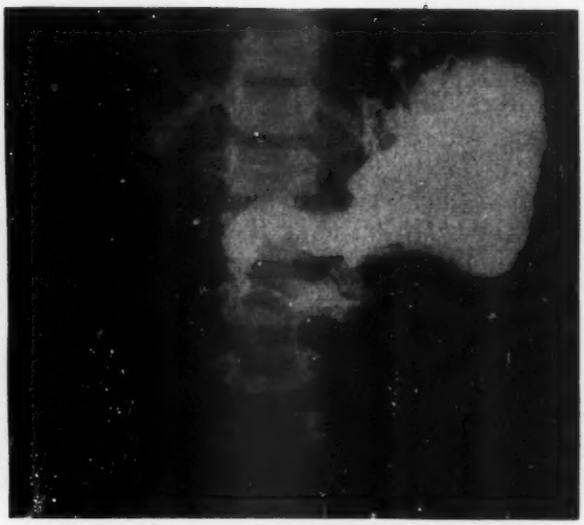

FIG. 2. Stomach and duodenum filled with barium showing coarsened mucosal folds of duodenum with obstruction after half an hour.

of the fourth portion of the (retroperitoneal) duodenum. The peritoneum over the mass was incised and all blood evacuated. Immediately following this the normal tone and color of the compressed and (proximal) distended bowel returned. Bleeding points were secured and the peritoneum was reapproximated. The abdomen was closed in layers without drainage.

The patient made an uneventful recovery and had a good bowel movement on the fourth postoperative day. He was discharged on the seventh day after operation.

COMMENTS

Hematomas have been described in all areas of the gastrointestinal tract [*2,4–10*]. They are most frequently associated with non-penetrating trauma to the abdomen. Blood dyscrasias are also known to be a predisposing factor [*9*]. There is a predilection for hematomas to occur in the retroperitoneal portion of the duodenum due to the relative fixation of the gut at this point. Trauma causes this portion of the duodenum to be pressed against the spine suddenly, and the disruption of the mesenteric attachments in this area initiates hemorrhage [*4*]. The hematoma forms between the serosa and muscularis, and the resulting mass causes obstruction [*4*]. This finding was evident in our case.

Felsen and Levin [*4*] consider the following roentgenographic findings to be characteristic of hematoma of the duodenum:

I. On the plain film:
   - A. A few distended loops in the left upper quadrant
   - B. An ill defined mass in the lumen of a distended loop of small bowel in the left upper quadrant
   - C. Obliteration or poor definition of the left psoas shadow

II. On gastrointestinal examination:
   - A. A space-occupying lesion 10 to 20 cm. in length involving the descending and transverse duodenum
   - B. Thickening of the mucosal folds in the proximal portion of the abnormal segment
   - C. Passage of the barium over the surface of a smooth, sharply marginated intramural mass which widens the lumen of the duodenum
   - D. Crowding of the valvulae conniventes producing a coil spring appearance. (Infiltration of blood or edema fluid into the mucosa occurs, thickening the valvulae conniventes and producing the enlarged folds seen radiographically. The cause of the coil spring pattern is not clear)
   - E. Evidence of extrinsic pressure on the greater curvature of the stomach and downward compression of the transverse colon
   - F. Obstruction

In our case some, but not all, of the criteria were found. There was a mass in the left upper quadrant of the abdomen, but air was seen only in the stomach and not in any distended loops of intestine. This, as well as the failure of the barium to pass over an intramural mass, was most likely due to the fact that there was complete obstruction at the transverse duodenum. The duodenal lumen was widened, however, and the mucosal folds were thickened.

SUMMARY

A surgically documented case of hematoma of the duodenum is presented. The preoperative x-ray studies fulfilled some of the diagnostic criteria reported in the literature and reviewed in this report.

Acknowledgment: We are grateful to Dr. Samuel Diener, Newark, New Jersey, for permission to report this case.

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The Imperforate Hymen As a Cause of "Abdominal Tumor"

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IMPERFORATE hymen which results in retention of menstrual discharge within the genital canal of a child at puberty has been reported as occurring about once in every 1,000 to 2,000 gynecologic admissions [*1,2*]. In a period of eighteen months three children were admitted to this hospital with this condition. A fourth case had been seen some years previously by one of us (A. H. R.). When these four children were first seen they all presented a large, lower abdominal mass which was diagnosed as follows: appendiceal abscess, incarcerated hernia, uterine malignancy and ovarian cyst. These diagnoses would have necessitated unnecessary and hazardous laparotomies. It occurred to us that it might be worthwhile to again call attention to the occurrence of this condition and to its simplicity of treatment by minor surgery.

CASE REPORTS

CASE I. A thirteen year old white girl was admitted because of abdominal fullness, and urgency and frequency of urination for two days. Abdominal examination revealed a doughy mass arising from the pelvis and extending to 3 cm. below the umbilicus. Rectal examination disclosed the entire pelvis to be filled with a cystic mass which was continuous with a sausage-shaped mass in the vagina. The hymen was imperforate and bulging. Hymenectomy was performed and about 700 cc. of dark blood was drained. The mass slowly subsided and she was discharged from the hospital two days later.

CASE II. An eleven year old white girl was admitted because of a lower abdominal mass which caused some vague discomfort for about one week. Abdominal examination showed a cystic, globular mass in the lower abdomen measuring approximately 12 cm. in diameter. Rectal examination revealed a sausage-shaped mass occupying the position of the vagina which reached from the introitus and merged with the abdominal mass. The hymen was imperforate and showed bluish discoloration with thickening in the midline. Hymenectomy was performed and about 600 cc. of dark, syrupy, bloody discharge was drained. She was discharged five days later.

CASE III. A fourteen year old white girl noted vague lower abdominal pain and increased tightness of her clothes for about six weeks prior to admission. Abdominal examination showed a doughy mass arising from the pelvis measuring about 14 cm. in diameter. Rectal examination disclosed the abdominal mass and the vaginal cystic mass to be continuous. The hymen was imperforate, dark blue in color and bulging. Hymenectomy was performed and approximately 800 cc. of black, thick bloody discharge was drained.

CASE IV. This was the patient who was seen some years ago. In 1950, when she was fifteen years old, she complained of cyclic pain and cramps in the right lower quadrant of the abdomen. These episodes occurred at about monthly intervals, the first having been about nine months prior to admission to the hospital. On examination there was a large, lower abdominal mass reaching almost to the umbilicus which felt cystic. Rectal examination disclosed a large, sausage-shaped mass filling the entire vagina and merging imperceptibly with the abdominal mass. The hymen was thickened,

bluish and bulging. Hymenectomy was performed and this was followed by first rapid and then slow spontaneous discharge of thick, chocolate-like, bloody discharge. She was dismissed from the hospital five days later.

Follow-up examinations during the next six years disclosed irregularity of menses along with small breasts, masculine distribution of hair and infantile uterus. The patient is now married and having coitus successfully, although there was some difficulty at first.

(When last seen in October, 1957 the patient was pregnant.)

COMMENTS

As is so common in a number of other conditions, the diagnosis can be made readily if it is but considered. There are few conditions in which observation of the external genitalia and rectal examination will make the diagnosis as easily as in this anomaly. The association of a child at the time of puberty who has not yet menstruated, with urinary symptoms, lower abdominal discomfort and a palpable mass in the lower abdomen necessitates inspection of the hymen and rectal examination. These procedures will disclose a bulging, imperforate hymen and a sausage-shaped mass, which fills the entire vagina and is continuous with the abdominal mass.

The treatment is incision of the hymen and excision or destruction of a sufficient portion of the hymen so that occlusion does not again occur when healing takes place. The internal genitalia are susceptible to infection due to the presence of old blood, a patulous cervix, an absence of vaginal acidity and the pressure effects on poorly developed epithelium. Certain precautions should be taken to minimize risk of infection. These are: strict aseptic technic, the avoidance of vaginal examination or the introduction of drains within the vagina, and no suprapubic pressure since the release of this pressure may cause suction of discharge back into the genital canal. The use of antibiotics prior to the operative procedure is in order. An enema should also be given prior to the surgery and the patient kept constipated for a few days afterwards to avoid contamination.

SUMMARY

This is a report of four cases of imperforate hymen which resulted in the appearance of a lower abdominal mass for which unwarranted laparotomies were contemplated. The diagnosis can be made with ease by the detection of an imperforate, bulging hymen and a sausage-shaped mass filling the vagina and continuous with the lower abdominal mass. The cure can be accomplished by simple hymenectomy.

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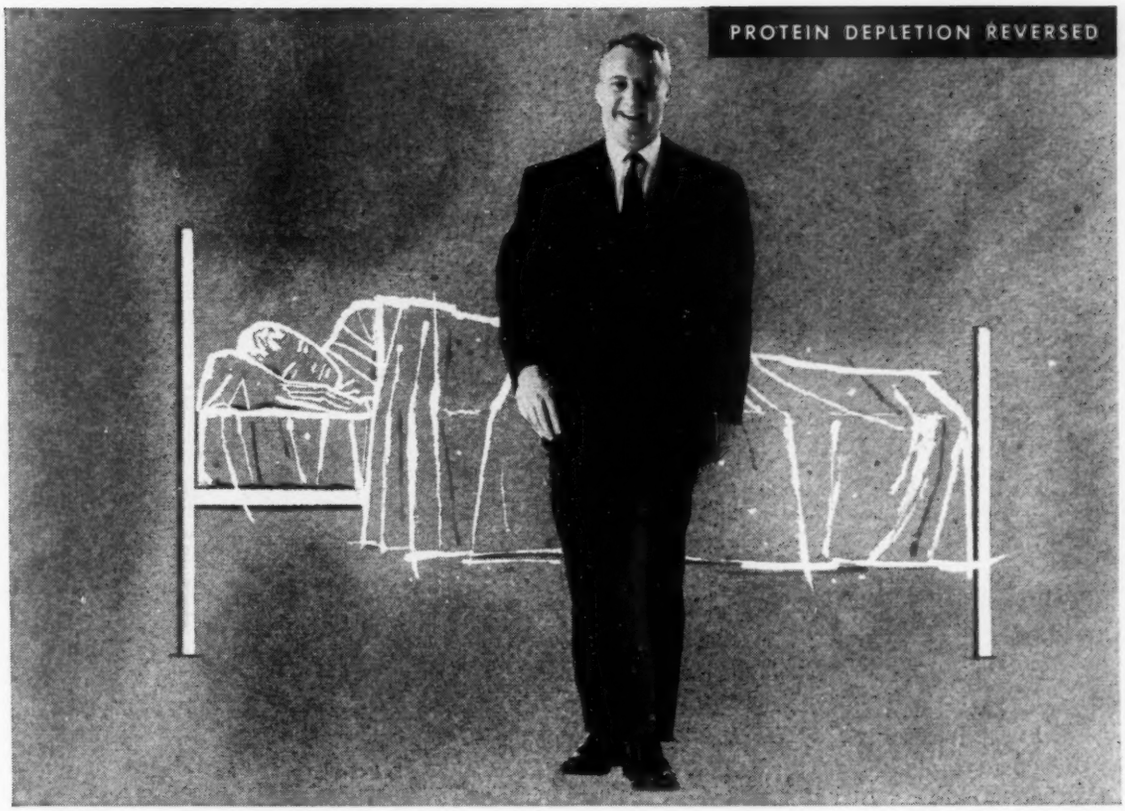

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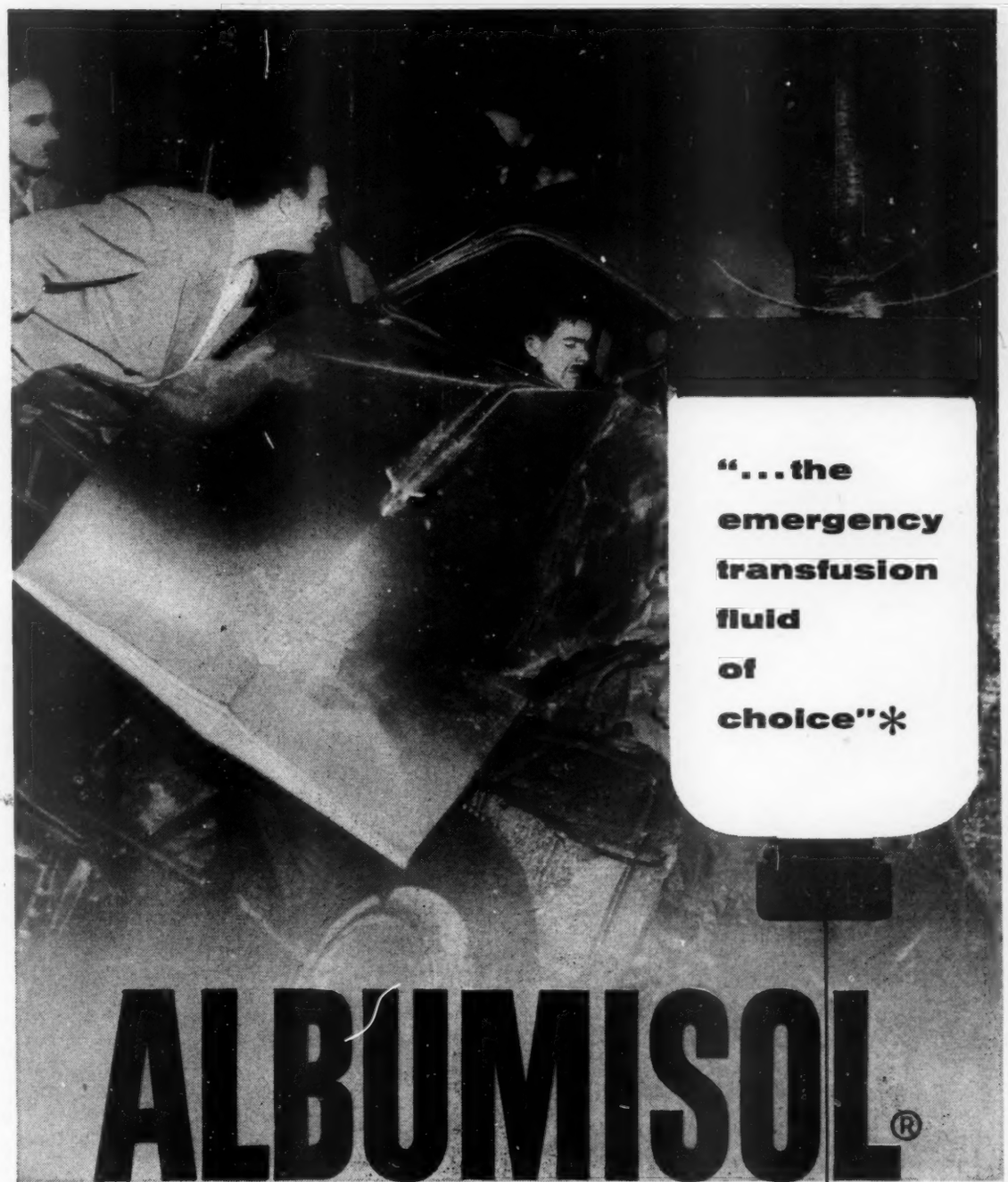

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*Janeway, C.A.: Quart. Rev. Med. 9:153 (Aug.) 1952.

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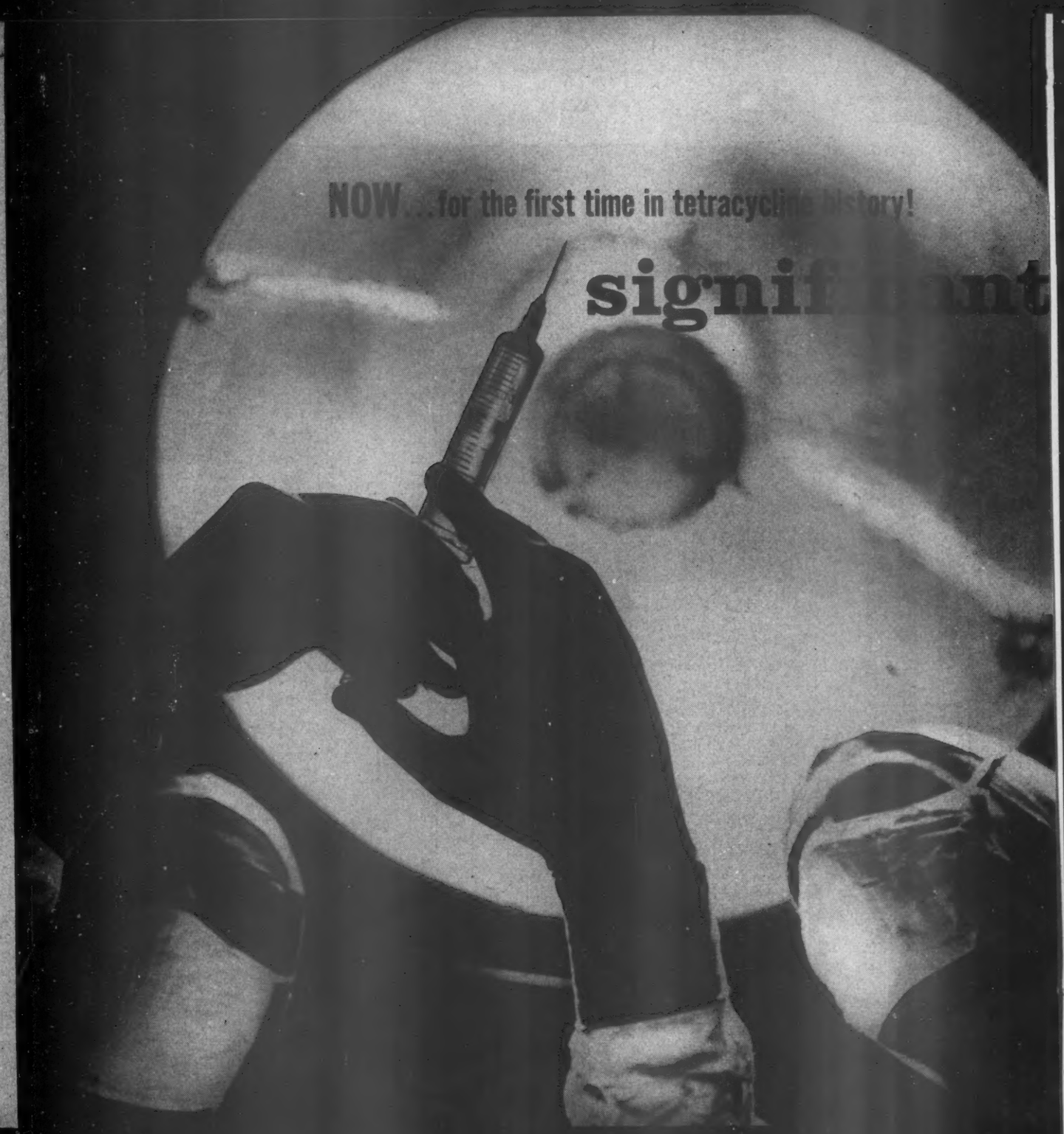

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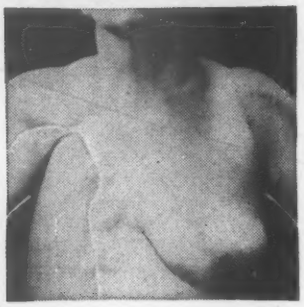

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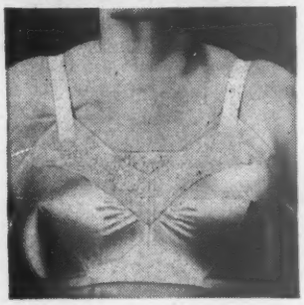

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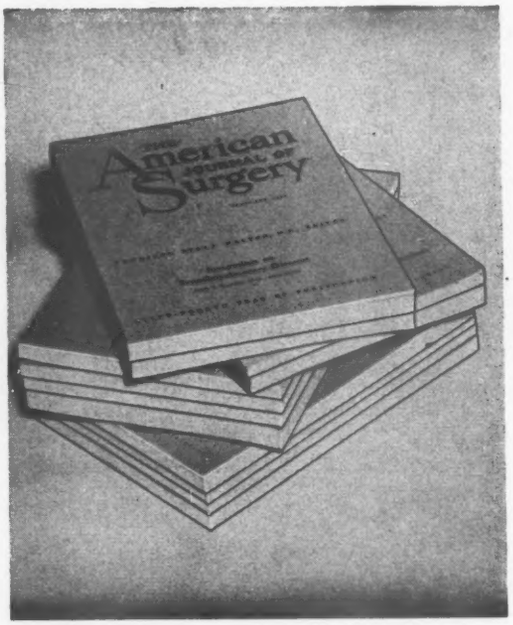

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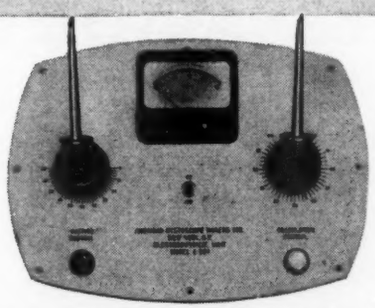

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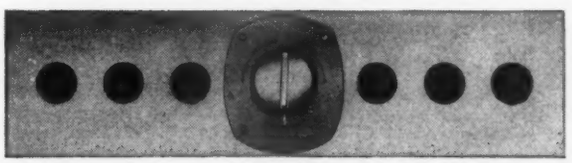

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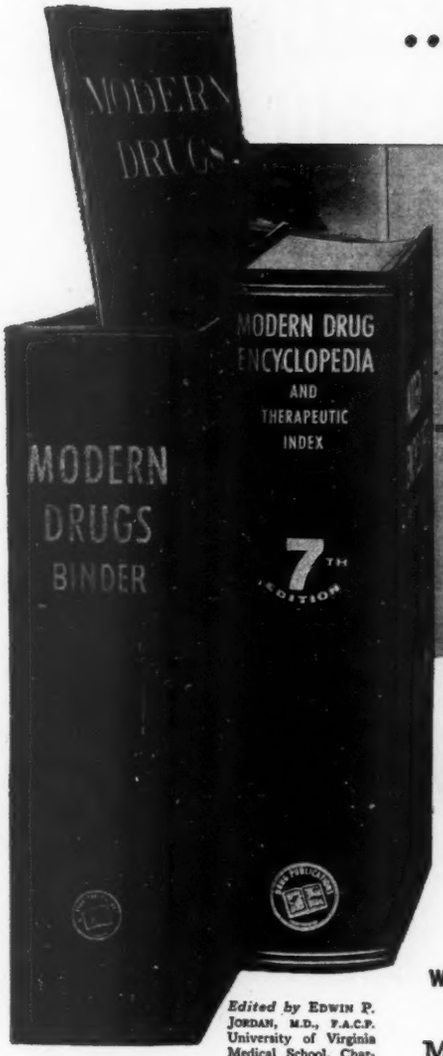

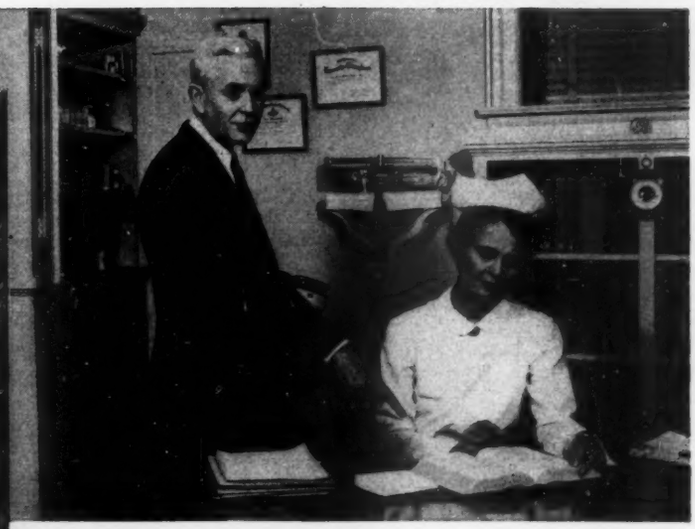

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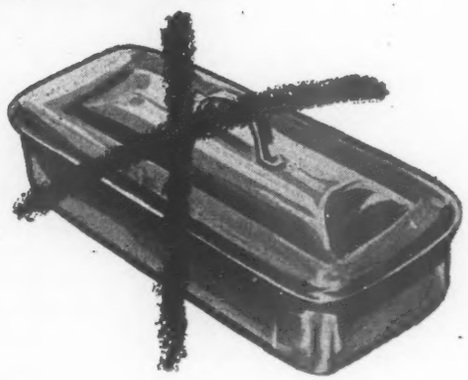

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NEW INTRINSIC FACTOR CONCENTRATE. Recent medical investigation has revealed that currently available drugs designed to increase the absorption of vitamin B_{12}, actually decrease the amounts absorbed in many cases. The substance necessary for the absorption of this important vitamin is intrinsic factor concentrate.

An improved vitamin B_{12} absorption test using radioactive cobalt-tagged vitamin B_{12} has demoustrated this inhibitory action of currently used intrinsic factor concentrates and enabled scientists at American Cyanamid Company's Lederle Laboratories, Pearl River, New York, to develop a new intrinsic factor concentrate which avoids this undesirable effect. The improved vitamin B_{12} absorption test was developed jointly by Dr. H. C. Lichtman of New York State College of Medicine's Kings County Hospital and Cyanamid's Research Division.

The new product, trademarked Autrinic by American Cyanamid Company, goes a step beyond former intrinsic factor concentrates since it augments absorption in all anemias whereas older forms were fully useful only in patients with pernicious anemia.

UNMASKING THE NARCOTIC ADDICT. *The long arm of advancing scientific research has found a drug with which to positively identify narcotics addicts.*

The new drug, called nalline,® is termed "an exciting new device in crime prevention" in a report of its initial use in the January-February issue of Listen, *a national journal of alcoholism and narcotics prevention.*

"Nalline is now compelling narcotics defendants to plead guilty," the journal's article, entitled 'Medicine Unmasks the Narcotics Addict,' says. "By using Nalline to expose and unmask these unfortunate young men and women, the police are in a position to offer aid while there is still time for recovery and rehabilitation."

One of the big problems facing police officers and agents in narcotics control enforcement is how to determine quickly and conclusively whether a suspect is or is not on drugs. Police know how cleverly suspects can hide their symptoms.

The new drug is related to sodium pentothol,® the "truth drug," in that it forces narcotics addicts to admit their addiction to drugs. Once administered, the drug causes immediate withdrawal symptoms in a suspect. "It is a wonder drug because it works conclusively and it tells the truth even when the addict tries to lie . . . By neutralizing morphine and other opium-related drugs, it acts as a narcotics antagonist and shows up the addict at once."

LAXATIVE-TYPE PRODUCTS. Introduction of dioctyl sodium sulfosuccinate products for relief of constipation has brought about a dramatic increase in prescriptions for laxative-type products, a survey conducted recently by Mead Johnson & Company indicates.

Before these products appeared on the market, prescriptions for laxatives and related products were declining at the rate of about 10 per cent a year, according to the survey. Currently, it shows prescription volume for laxatives running 75 per cent ahead of two years ago.

The year-long Mead Johnson survey, which was tied in with an independent prescription audit, was designed to measure the impact of Colace and Peri-Colace, the firm's new dioctyl sodium sulfosuccinate products.

Responsible for this striking upturn in laxative prescriptions is a widespread new interest among doctors in the professional management of constipation.

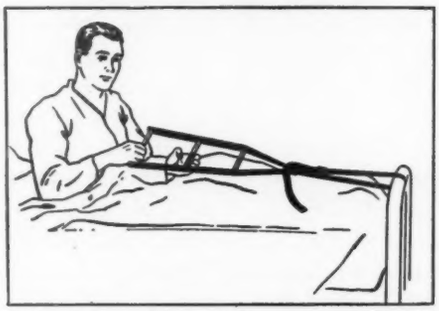
BLAKSLEE AWARDS COMPETITION. *The American Heart Association has announced the opening of the sixth annual competition for the Howard W. Blakeslee Awards for outstanding reporting in the field of heart and blood vessel diseases. The Heart Association's Awards Committee will make its selections from among newspaper and magazine articles, books, radio and television programs and films published or produced between March 1, 1957 and February 28, 1958. The deadline for entries is May 1, 1958.*

Entries submitted by local daily or weekly newspapers, and local radio and television stations will be considered on the same basis as entries from national wire services, syndicates or radio-TV networks, and they will be eligible for awards in separate categories. The number of winners to be selected will be determined by the judges.

The Awards, which carry an honorarium of

CONTINUED ON PAGE 52

For Patient Protection



The New Posey "Patient Aid"

The new Posey "Patient Aid" is another rehabilitation product which encourages self-exercise and is a positive aid to the geriatric. The patient can raise himself without calling for the nurse.
Catalog #B-654 (For open end beds) $5.95 each. Catalog #B-654A (For beds with solid foot ends) $5.95 each.

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CAMP ARM SLING
for men, women and children

The new Camp arm sling offers these advantages: (1) supports the weight of the injured arm on the opposite shoulder (2) has a special tie feature which prevents arm dangling when the patient stoops and (3) support from the uninjured shoulder eliminates pull on the cervical spine. Available for right or left arms in extra small, small and medium sizes. In sturdy gray fabric.

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$500 each, will be presented in the fall. Entry blanks and rules folders may be obtained from local Heart Associations or from the American Heart Association, 44 E. 23rd St., New York, N.Y.

ELECTRON BEAM STERILIZATION. Research on electron beam sterilization of sutures was started by Ethicon, Inc. in 1949 in collaboration with High Voltage Engineering Corporation. The preliminary work suggested that sutures could be sterilized without significant damage to the product. Intensive research began with the acquisition of a 2 MEV Van de Graaff Accelerator by Ethicon in 1953. The minimal radiation dose to kill a wide variety of bacteria, yeasts and molds was established. The effect of various factors such as temperature, presence or absence of chemicals, age of microbial cultures, etc. were studied. The effect of radiation on the suture and various containers—as compared to other methods of sterilization—was established. Finally, the effect of radiated sutures in animals and in human beings was studied in cooperation with numerous surgeons at leading medical centers.

Traditionally, surgical sutures have been sterilized by heat. No particular problems exist with heat sterilization of non-absorbable sutures such as silk, cotton, steel, tantalum, etc. However, catgut (derived from the submucosal layer of sheep intestines or the serosal layer of beef intestines) is a protein and is damaged (literally "cooked") by heat. To minimize this damage, it is necessary to dry the sutures thoroughly and then heat-sterilize them to 312°F. for one hour in open-ended tubes. The sterile sutures then must be handled aseptically, with the same precautions as are taken in a hospital operating room, tubing fluid (sterile 90 per cent isopropyl alcohol) added, and the tubes sealed. Extraordinary precautions in handling these sutures from the time of sterilization to the final sealing of the tube are necessary to prevent accidental contamination. Electron beam sterilization eliminates the heat and the aseptic handling since sterilization is accomplished after addition of the tubing fluid and sealing of the tubes. This fact in itself assures the surgeon of increased safety and reliability of the product.

Of equal significance is the fact that catgut sutures lose from 10 to 20 per cent of their original tensile strength after heat sterilization. They also lose pliability and tend to be somewhat stiff. Electron beam sterilization results in a tensile strength loss of only 4 to 8 per cent which means that electron beam sterilized sutures are, on the average, 8 to 14 per cent stronger than heat-sterilized sutures. In addition, electron beam sterilized sutures do not lose their pliability. They are easier for the surgeon to handle in the operating room.

All forms of bacteria, yeasts and molds are killed by electron beam radiation. The dose necessary to kill varies with the form of the organism and the species. Spore forms of such organisms as tetanus and gas gangrene bacteria are most resistant.

Ethicon, Inc. is the first company in the world to subject the major portion of its production to electron beam sterilization and in so doing becomes one of the first companies to put to peaceful use the tremendous power of atomic particles.

A NEW APPETITE-SUPPRESSANT. *A group of obese persons with diabetes consistently lost weight for the first time when a new appetite-suppressant drug was added to their diet, it is reported by Dr. Rosario Robillard of Montreal.*

Called 'Preludin' (Geigy Pharmaceuticals), the drug "seems free of all disturbing effects and its results are promising" (Canad. M. J. *76: 238, 1957*).

Results of the study on fifty-one obese persons with diabetes showed an average weight reduction of 1.01 pounds per week. The treatment period varied between two and twenty-six weeks, with a mean of 10.3 weeks.

BARD-PARKER STERILE BLADE PACKAGE. Bard-Parker Company of Danbury, Connecticut announces the availability of their new sterile blade package. The unit consists of a sterile B-P Rib-Back blade of carbon steel, heat-sealed in a moisture-proof and puncture-resistant envelope that can be autoclaved. The easily opened reenforced envelope permits the nurse to attach the knife handle to the blade while in the opened package. B-P sterile-packaged blades come in all sizes in 1 gross boxes.

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The predominant symptom for which a majority of patients seek medical help.
For nerve block control of neuralgic phases of somatic pain, SARAPIN, the aqueous non-toxic distillate of Pitcher Plant has been used successfully by clinicians throughout the country for nearly a decade.

An extensive discussion giving details of the technique of regional analgesia may be found in our booklet "Sarapin, Injection Technique in Pain Control," and is available on request.

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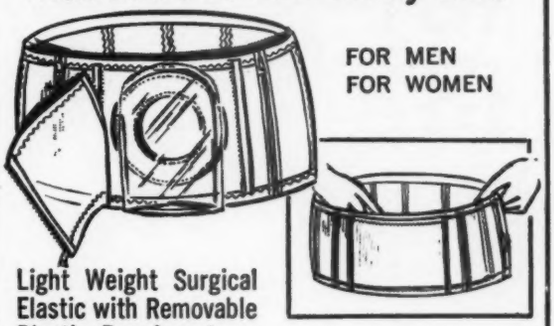

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101 out of **106**

infected wounds successfully treated with

Panafil®

OINTMENT

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Papain—effective debriding enzyme, gently and safely removes debris and slough detrimental to the healing process.

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Chlorophyll derivatives—control inflammation, promote the growth of normal, healthy granulations.

PANAFIL Ointment contains papain 10%, urea U.S.P. 10%, and water-soluble chlorophyll derivatives 0.5% in a hydrophilic ointment base. Available in 1-ounce and 4-ounce tubes *on prescription only*.

Miller, J. M.; Godfrey, G. C.; Ginsberg, M., and Papastrat, C. J., in Surgical Service, V. A. Hospital, Fort Howard, Maryland: Postgrad. Med. *22*:609, 1957.

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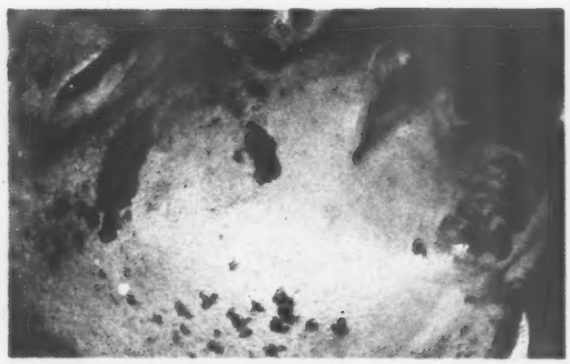
Case #1 Left cheek untreated



Case #1 Right cheek, after treatment with Adrenosem

Case #2 Left cheek untreated

Case #2 Right cheek, after treatment with Adrenosem

Write for literature describing the action and uses of Adrenosem Salicylate

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